THE CARBON COMPOUNDS

A TEXTBOOK OF ORGANIC CHEMISTRY

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PREFACE

This volume constitutes an outline of an elementary course in organic chemistry as presented to sophomore students in the University of California. The scope of the book is limited to a presentation of fundamental principles and general reactions. Some of the doctrines of the electron theory; postulates concerning the origin of color; and views relating to free radicals are included. The author realizes that the conclusions based upon these recent contributions may require early revision, but it is important to stimulate interest in the researches of today even if in doing so we introduce here and there a theory of no permanent value. The responsibility rests upon the teacher to make such revisions and additions as may be necessary to give the student an acquaintance with new developments that may modify the views expressed in these pages.

The book has three main divisions. The first part is devoted to the aliphatic compounds; the second deals with the aromatic compounds; and the third constitutes a review of the more important general organic reactions.

The text includes many references to recent contributions and to discussions presented in the following books: Meyer and Jacobson, Lehrbuch der Organischen Chemie; Richter, Chemie der Kohlenstoffverbindungen; Beilstein, Handbuch der Organischen Chemie; Sidgwick, Organic Chemistry of Nitrogen; Cohen, Organic Chemistry; Weyl, Die Methoden der Organischen Chemie; Pictet, The Vegetable Alkaloids; and Mulliken, Identification of Pure Organic Compounds. The list is given here not only as an acknowledgment of indebtedness to the authors but also for the purpose of directing the attention of the student to a very valuable group of reference books.

In preparing this outline the author has had the advantage of constructive criticism from Professors T. D. Stewart and G. E. K. Branch of the University of California, and from Professor F. W. Upson of the University of Nebraska.

C. W. PORTER

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AROMATIC COMPOUNDS

ABBREVIATIONS

The abbreviations adopted by the American Chemical Society are used in this book. For complete list see "Chemical Abstracts," Vol. 14, No. 24 (Dec. 20, 1920). Titles of journals are abbreviated as follows:

Am. Chem. J. The American Chemical Journal.
Am. J. Med. Sci. The American Journal of Medical Sciences.
Am. J. Sci. The American Journal of Science.
Ann. Annalen der Chemie (Liebig's).
Ann. chim. phys. Annales de chimie et de physique.
Ber. Berichte der deutschen chemischen Gesellschaft.
Chem. Zentr. Chemisches Zentralblatt.
Chem. Zeit. Chemiker Zeitung.
Compt. rend. Comptes rendus de l'académie des sciences.
Gazz. chim. ital. Gazzetta chimica italiana.
J. Am. Chem. Soc. The Journal of the American Chemical Society.
J. Am. Med. Assoc. The Journal of the American Medical Association.
J. Chem. Soc. The Journal of the Chemical Society (London).
J. Phys. Chem. The Journal of Physical Chemistry.
Monatsh. Monatshefte für Chemie.
Phil. Mag. The Philosophical Magazine and Journal of Science (London).
Z. physik. Chem. Zeitschrift für physikalische Chemie.

THE CARBON COMPOUNDS

INTRODUCTION

Organic Chemistry is the division of science that deals with the compounds of carbon. There are no definite boundaries in nature that establish the realm of organic chemistry in such a way as to distinguish it from inorganic, analytical, or other divisions of the subject; nor are there natural boundaries between broader fields of science, such as chemistry, physics, and biology. All such classifications are more or less artificial and the limits are arbitrarily fixed so as to group closely related phenomena for convenience of treatment.

The use of the terms *organic* and *inorganic* as applied to chemistry developed as a result of attempts to classify chemical substances on the basis of origin. All compounds formed in the tissues of living organisms — plants and animals — were called organic. These compounds were found to be more complex in character than those found in the mineral kingdom, and the early chemists were convinced that such compounds could be synthesized only through the operation of vital forces. They believed that only through the agency of life could the compounds found in living tissue be produced from inorganic sources.

It is still customary to attribute to vital forces many phenomena that cannot be reproduced by artificial means; but the element of mystery is rapidly disappearing and every year experimental methods are developed to make new inroads upon the domain of "vital forces." Already hundreds of compounds, occurring in nature only in living organisms, have been synthesized from inorganic sources in the apparatus of the laboratory. They have been built up through applications of the general laws of physics and chemistry, without the intervention of mysterious forces. The majority of these

compounds contain carbon; and due to certain peculiarities of carbon, recognized only within the last century, the study of these compounds seemed hopeless to the earlier investigators.

Carbon compounds, as a rule, are non-polar. Their reactions are molecular, not ionic. Most of the carbon compounds are more soluble in alcohol, ether, benzene, or chloroform than in water. Reactions between carbon compounds generally require considerable time (from a few minutes to several days) for their completion or for the establishment of equilibrium, whereas the ionic reactions of inorganic chemistry are often completed in a fraction of a second. Carbon is unique in its capacity to form compounds of high molecular weight and of great diversity in molecular structure, many carbon atoms being linked together in continuous and in branched chains within a single molecule.

To assign definite structures to the molecules of carbon compounds and to devise means for reproducing these structures experimentally was the ambition of many of the best chemists of the last century. Their success in this work established the structure theory, and made it evident that the chemical and physical properties of compounds are determined, not by composition alone, but also by the arrangement of the atoms in the molecules.

Since chemical and physical properties are determined by the configuration or structural arrangement of the atoms within the molecule, it is possible to have many different compounds of identical composition and molecular weight. The existence of two or more compounds having the same empirical formula — differing from each other only in the way the atoms are grouped or arranged in space — constitutes isomerism. It is almost exclusively a property of carbon compounds. One hundred thirty-five compounds having the formula $C_{10}H_{13}O_2$ have been discovered, and this is hardly an exceptional case. It is the rule, rather than an exception, to have many different compounds represented by the same molecular formula.

Such features have made necessary the development of special methods of investigation involving a laboratory technique essentially different from that required in inorganic work. We are, therefore, justified in studying the carbon compounds as a separate branch of chemistry; and we now define organic chemistry as the chemistry of the carbon compounds.

We retain the term *organic*, although the subject has outgrown its original meaning; and we retain also the subject matter originally assigned to this field; for, since practically all of the compounds of living matter contain carbon, the substances and types of reactions originally referred to as organic fall logically within the scope of the newer definition.

Approximately 230,000 compounds of carbon are known. The vast majority of these contain carbon with one or more of the following elements: hydrogen, oxygen, nitrogen, sulphur, chlorine, bromine, iodine, phosphorus.

The practical methods used to purify and identify these substances, as well as the methods of analysis, are explained in detail in laboratory manuals and need not be given here. The principles underlying the analytical procedures are very simple, but it requires skill in the manipulation of apparatus to secure accurate results.

Carbon and hydrogen are determined by oxidizing the sample with hot copper oxide. The hydrogen contained in the sample is converted quantitatively into water, which is absorbed by calcium chloride or sulphuric acid, and weighed. The carbon of the sample is simultaneously converted into carbon dioxide, which is absorbed by potassium hydroxide solution, and weighed. When an organic nitrogen compound is decomposed by hot copper oxide, and the resulting gases are passed over hot metallic copper, nitrogen escapes in the free state. The gas is collected, freed from carbon dioxide by means of sodium hydroxide, and finally measured in a gas burette over water or mercury. A qualitative test for nitrogen is made by heating the compound with sodium and testing the product for cyanide ion. An aqueous extract of the fused mass is treated with ferrous and ferric sulphates, then acidified. A blue precipitate of ferrous-ferric cyanide reveals the presence of nitrogen. The reactions may be represented as follows:

$$\text{Carbon nitrogen compound} + Na \longrightarrow NaCN.$$
$$6CN^- + Fe^{++} \longrightarrow Fe(CN)_6^{----}.$$
$$4Fe^{+++} + 3Fe(CN)_6^{----} \longrightarrow Fe_4[Fe(CN)_6]_3.$$

A substance to be analyzed for sulphur is oxidized by concentrated nitric acid at 300° C. in a sealed tube. The sulphur is converted into sulphuric acid. Barium chloride is added and the sulphur is estimated from the weight of barium sulphate

precipitated. In the same way phosphorus is converted into phosphoric acid, then estimated by the usual inorganic procedure. Halogen compounds are heated in sealed tubes with fuming nitric acid and solid silver nitrate. The silver halide formed is washed and weighed. A combustion method for analyzing halogen compounds has been developed by Reid. The halogen is absorbed by a mixture of powdered silver and silver oxide.*

Classification. Organic compounds are classified as *aliphatic* or *aromatic*. The division referred to as aliphatic comprises the compounds in which the carbon atoms are linked together in open chains or rows. The name originally applied to the fats (ἄλειφαρ, fat). The fats now constitute only a minor group in the aliphatic division. The term *aromatic* was originally applied to compounds characterized by agreeable aromas. Almond oil, cinnamon, and vanilla were among the natural products originally classified as aromatic. Most of the compounds that were grouped together on the basis of odor are derivatives of benzene, and now, without reference to odor, all derivatives of benzene are said to belong to the aromatic series. In benzene and in each of its homologues there is a closed chain or ring of carbon atoms. The members of the aromatic series, therefore, are often referred to as cyclic compounds.

Homology. The study of organic chemistry is simplified by the fact that its thousands of compounds fall into a comparatively few groups or classes. The individual members in a class have certain properties in common. In many cases the compounds constituting a class are so related that, when arranged in the order of their molecular weights, there is a constant difference in composition between successive members. Such a group of compounds constitutes a homologous series. We have, for example, the hydrocarbons methane, CH_4; ethane, C_2H_6; and propane, C_3H_8. The difference in composition between successive members is CH_2. Corresponding to this difference in composition and molecular weight, there is a gradual change in properties such as density, solubility, and capacity to act with certain reagents. From the characteristics of a few of the lower, intermediate, and higher members of a homologous series we learn the trend in physical and chemical properties as applied to the group. We can then predict, with fair precision, the properties of any individual compound in the series.

* Reid, *J. Am. Chem. Soc.*, **34**, 1033 (1912).

Isomerism. Compounds having the same elementary composition and the same molecular weight, yet differing in chemical and physical properties, are known as isomers. Since isomers have the same empirical formula, the differences in properties must be due to different orientations of the atoms within the molecules. Ethyl alcohol and methyl ether have the formula C_2H_6O. The arrangements of the atoms in the two molecules are represented by the structural formulas $CH_3—CH_2OH$ and $CH_3—O—CH_3$. In the alcohol the two carbon atoms are held together by a direct valence bond. In the ether an oxygen atom intervenes between the carbon atoms. In the alcohol there is a hydroxyl group. In the ether there is no hydrogen atom attached to oxygen. These structural details account for the chemical and physical properties of the two compounds. Two hydrocarbons having the same empirical formula, C_4H_{10}, are represented by the following graphic or structural formulas:

$$CH_3—CH_2—CH_2—CH_3 \text{ and } \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH—CH_3.$$

There are other types of structural differences that give rise to isomerism. Asymmetric molecules, as much alike as an object is like its own mirror image, are not identical in properties. Such pairs of compounds have similar groups attached to corresponding atoms in the molecules, but the positions of these groups in space are not identical. The molecules constituting the pair are different in the same sense that the right and left hands are different. These are known as space isomers or stereoisomers. Another type of isomerism is displayed by some unsaturated compounds. An unsaturated compound is characterized by the presence of a double or triple bond. At some point in such a compound two or more valence bonds are exercised in holding together two adjacent atoms. Changes in the positions of atoms or groups with respect to the multiple bond may give rise to isomers. Any variation in the arrangement of the atoms in a molecule imparts new properties to the compound. Many examples will be considered in detail later.

Valency. The beginner in organic chemistry often finds it difficult to account for the behavior of carbon in its capacity to combine with either electro-positive or electro-negative elements. In this connection a brief consideration of the more important theories of valence may be helpful.

Although Dalton, as early as 1804, announced his opinion that molecules are formed through the union of indivisible units, which he called atoms, no useful theory of valence was advanced until Frankland recognized the fact that each atom has a definite saturation capacity and that this capacity may be measured in terms of the number of hydrogen atoms or hydrogen equivalents of other elements with which it will combine.*

The earliest physical interpretation of valence involved the assumption that there were a certain number of points or projections on the surface of each atom admitting of mechanical attachment to corresponding points on other atoms.

According to a later view, presented by Werner, valence is a force of attraction emanating from the center of the atom and uniformly distributed over its surface. In the formation of compounds, according to Werner, atoms are drawn into groups with such symmetry of packing as will produce the maximum neutralization of their reciprocal affinities. The most stable arrangement is represented by a structure in which the central atom is completely covered by others without their overlapping. If all the atoms attached to a given carbon atom are alike, as in CH_4, each will have an equal share of the surface of the central atom, and their distribution will correspond to the four points of a regular tetrahedron. If the attached atoms or groups are not alike, the tetrahedral form will be distorted, some groups being held by more and others by less than one fourth of the total affinity. According to this view it is not necessary to have four atoms attached to each carbon to produce saturation. A smaller number of large groups might cover an atom and neutralize its surface attraction. In this way Werner accounts for the existence of compounds like triphenylmethyl. The atoms are assumed to be spherical and the full influence of the attraction emanating from the center is exerted only at the point of contact with another atom. Thus two spherical atoms represented by circles

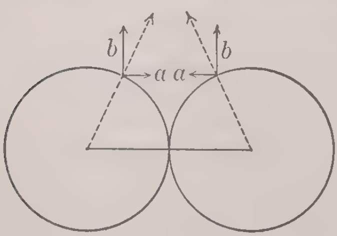


FIG. 1

in Figure 1 are held by the undiminished force represented by a line joining their centers, and by the resultants parallel to this

* Frankland, *Phil. Trans.*, **142**, 417 (1852).

line of an infinite number of other attractive forces radiating from the center of the atom. Of the forces indicated by dotted lines only the components marked *a* serve to hold the atoms together.

Werner assumes that in unsaturated compounds the surface attraction is not uniformly distributed, but on each carbon atom of the so-called unsaturated pair it is more or less concentrated on the hemispheres facing each other. To avoid the implication that such union should be firmer than that between carbon atoms in a saturated compound he makes a distinction between the stability and the activity of a compound. The activity of a compound is determined by its residual valence (component *b*), and this component is larger in unsaturated than in saturated compounds. Carbon is said to be completely saturated when combined with four univalent radicals. The total amount of affinity of the carbon atom may not be exhausted, however, when four groups are attached. The compound so formed may be able to hold quite firmly one or more molecules of water, ammonia, or other so-called saturated compounds through the exercise of residual valence.

Modern conceptions of valence are based upon the properties of electrons. It is an accepted doctrine that chemical bonds are established through definite mutual relations between electrons in the outer energy levels of the atoms concerned. This principle applies whether we assume that the electrons in an atom are revolving in orbits corresponding to different energy levels or whether we assume that the electrons occupy relatively fixed positions in concentric shells around the positive nucleus.

The most exact measure of valence is based upon the quantity of electricity transported in the process of liberating from a compound, by electrolysis, one atomic weight of the element. One faraday (96,494 coulombs) is associated with every univalent gram-ion, and twice that quantity with every bivalent gram-ion, and so on. The number of faradays of electricity carried by one atomic weight of an element corresponds exactly to its valence as determined by other methods, and this justifies the conclusion that elements in compounds are bound together by electrical forces.

It is customary in inorganic chemistry to specify the positive or negative character of the valence of an element. In barium chloride, for instance, the barium ion, Ba^{++}, is said

to have a valence of +2 and each chloride ion, Cl^-, a valence of −1. These values are logically assigned on the basis of the behavior of barium chloride solutions when subjected to electrolysis. The sign of the charge is definitely determined by the direction of its migration when conducting a current; and its numerical value corresponds to the number of faradays carried by the gram-atom or gram-ion. Carbon compounds, as a rule, do not ionize. If the valence of hydrogen is taken as +1 and that of chlorine −1, as determined from the electrolysis of hydrochloric acid, then carbon exhibits a valence of +4, or −4, or any intermediate value; for we have such compounds as CH_4, CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4. But if a compound is non-polar to the extent that it does not ionize, there is no necessity for assigning to its atoms polar valences. In most of the typical organic compounds we will regard carbon as having a valence of four. This represents its saturation capacity as determined by its ability to hold other elements or groups; but we will not specify the polar character of this valence except in cases where electrochemical properties are displayed in one form or another.

The discovery that electricity is atomic in character and that electrons — atoms of electricity — are constituents of all other forms of matter led immediately to speculations concerning atomic structures. As an outgrowth of these studies we have a theory of valence lacking very little of being an established fact; and this theory postulates that it is the orientation of atoms of electricity that determines the nature of the chemical union between elements. The electron is too small to be seen with the aid of the most powerful microscope. It is, in fact, hopelessly beyond the range of human vision, for it is too small to cause interference with the shortest wave that the eye interprets as light. Nevertheless, it has been isolated and weighed, and the magnitude of its charge has been measured.* It can be derived from any of the ordinary chemical elements. It is the unit charge of negative electricity.

The chemical atom of any element consists of a positive nucleus associated with a sufficient number of electrons to make the atom, as a whole, electrically neutral. The atoms of different elements have different masses; different quantities of matter in their positive cores and different numbers of

* Millikan, The Electron, University of Chicago Press.

electrons. The number of electrons in an atom of any element, as determined by an investigation of X-ray spectra, was found by Moseley* to correspond, in nearly every case, to the ordinal number of the element in the periodic system.

An ordinary spectrum of visible light is produced by means of a grating in which the distance between rulings is of the order of the wave length of light. The wave length of an X-ray is approximately a thousand times shorter than the average length for visible light waves. It is not possible to rule lines on glass close enough together to cause diffraction of such waves. The smooth surface of a crystal of almost any salt furnishes a natural grating suitable for this purpose. In the growth of the crystal the separate particles are laid on in rows with such uniformity and so close together that the layers of atoms serve as gratings for X-rays. The X-rays are produced in an evacuated tube by allowing cathode rays (streams of electrons) to impinge upon a target (anticathode) consisting of the element under investigation. When all other conditions are kept constant, the wave length of the X-ray produced at the anticathode may be changed by changing the element used as a target. Each element produces a characteristic X-ray spectrum. Elements of highest atomic weights produce X-rays of shortest wave lengths. By arranging the elements in the order of decreasing wave lengths, the ordinary periodic system is almost duplicated, and to each element in this modified table a whole number can be assigned which not only indicates the position of the element in the table but is inversely proportional to the square root of its characteristic X-ray frequency.

ATOMIC NUMBERS

H 1	He 2	Li 3	Gl 4	B 5	C 6	N 7	O 8	F 9			
	Ne 10	Na 11	Mg 12	Al 13	Si 14	P 15	S 16	Cl 17			
	A 18	K 19	Ca 20	Sc 21	Ti 22	V 23	Cr 24	Mn 25	Fe 26	Co 27	Ni 28
		Cu 29	Zn 30	Ga 31	Ge 32	As 33	Se 34	Br 35			
	Kr 36	Rb 37	Sr 38	Y 39	Zr 40	Cb 41	Mo 42	– 43	Ru 44	Rh 45	Pd 46
		Ag 47	Cd 48	In 49	Sn 50	Sb 51	Te 52	I 53			
	Xe 54	Cs 55	Ba 56	La 57	Ce 58	Ta 73†	W 74	– 75	Os 76	Ir 77	Pt 78
		Au 79	Hg 80	Tl 81	Pb 82	Bi 83	Po 84	– 85			
	Nt 86	– 87	Ra 88	Ad 89	Th 90	Ut 91	U 92				

* Moseley, *Phil. Mag.*, **26**, 1024 (1914).

† The atomic numbers 59–72 are those of the metals of the rare earths: Pr 59, Nd 60, – 61, Sa 62, Eu 63, Gd 64, Tb 65, Dy 66, Ho 67, Er 68, Tm 69, Yb 70, La 71, – 72.

The Bohr Atom. In order to connect Planck's theory of radiation with an electronic structure of the atom, Bohr * assumes that the electrons are in orbital motion around the positive nucleus of the atom. The theory finds splendid support in the domain of spectroscopy. Assuming that radiation occurs only when an electron moves from one orbit to another, it is possible to account for the complex spectra of many of the elements in a very satisfactory way. From the standpoint of structural organic chemistry this picture of the atom is not wholly satisfactory, and the remarkable theory of Bohr, that has been so productive in the field of physics, will not be presented here.

The Lewis Atom. A theory of atomic structure that is more readily applied in the interpretation of chemical phenomena is that proposed by G. N. Lewis † and amplified by Langmuir.‡ It is assumed that:

1. "In every atom there is a kernel which remains unaltered in chemical changes and which possesses an excess of positive charges corresponding in number to the ordinal number of the group in the periodic table to which the element belongs."

2. "The atom is composed of the kernel and an outer shell, which, in the case of a neutral atom, contains negative electrons equal in number to the excess of positive charges of the kernel, but the number of electrons in the shell may vary during chemical change between zero and eight."

3. "The atom tends to hold an even number of electrons in the shell and especially to hold eight electrons (an octet) which are normally arranged symmetrically at the corners of a cube or at the points of a tetrahedron." §

4. "Two electronic shells are mutually interpenetrable."

5. "Electrons may ordinarily pass with readiness from one position in the outer shell to another. Nevertheless, they are held in position by more or less rigid constraints, and these positions and the magnitude of the constraints are determined by the nature of the atom and of such other atoms as are combined with it."

* Bohr, *Phil. Mag.*, **26**, 857 (1914).

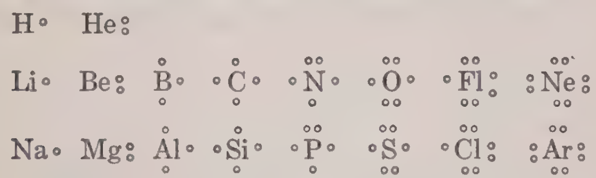
† Lewis, *J. Am. Chem. Soc.*, **38**, 762 (1916).

‡ Langmuir, *J. Am. Chem. Soc.*, **41**, 868 (1919).

§ Hydrogen and helium tend to hold two electrons instead of eight. The neutral hydrogen atom has one electron, so that the introduction of one additional electron into the hydrogen shell is analogous to completing the octet in the electronic shell of another atom.

6. "Electric forces between particles which are very close together do not obey the simple law of inverse squares which holds at greater distances."

If we represent the nuclei of the elements by the symbols ordinarily used for the neutral atoms, and use small circles to indicate the electrons in the outer shells of the atoms, then, following the order of the periodic system, we have:



Argon differs from chlorine in possessing an additional positive charge in the nucleus and one more electron. It, therefore, has a complete octet and is at the same time electrically neutral, hence, like helium with its pair, and neon with its octet, argon displays zero valence. The next element in the periodic table, potassium, may be regarded as possessing the argon group with one additional positive charge within the nucleus and one electron in an outer or valence shell. The total number of electrons in the potassium atom, exclusive of those present in the nucleus, is 19; but only the single electron in the outer shell can take part in the formation of a valence bond. It may give up this electron and become a positively charged potassium ion. It never appears in the rôle of an electronegative element by taking electrons from other elements. Carbon has four electrons in the outer shell. It may give up these four negative charges and function as an element having a valence of +4 (as in CCl_4), or it may acquire four additional electrons to complete its octet and in this case function as an element having a valence of −4 (as in CH_4). Chlorine has seven electrons in the outer shell. It may take up one more to form the negative univalent chloride ion.

Now, what happens when neutral solid potassium and neutral gaseous chlorine combine to form a salt? The majority of the chemists of to-day say that on account of the strong tendency of the chlorine atom to acquire an additional electron and a corresponding tendency on the part of potassium to give up one, an electron passes from potassium to chlorine, establishing a positive charge on the metal and a negative charge on the

halogen. The two oppositely charged units are then held together as a result of the electrical force of attraction existing between them. According to this view a chemical bond, or valence bond, between two elements is an electrical force established by the passage of an electron from one element to another.

In non-polar compounds, including most of the carbon compounds, it is assumed that the valence electrons do not pass completely from one atom to another but take positions between the two nuclei and are shared by them. According to this view, one or both of the combining atoms may contribute to the establishment of a stable group (usually a pair) of electrons between the two elements. Similar electronic structures exist in polar compounds, but in these there is considerable difference in the tendencies of the atoms to hold or to yield electrons, so that dissociation may occur with more electrons in one ion and less in the other than are present in the corresponding neutral elementary atoms. In such cases we are justified in speaking of an electron as passing from one atom to another; but even in highly polar compounds the undissociated molecules probably represent structures in which the valence electrons are shared (though not equally) by the two atoms that are united through the bond in question.

The earliest announcement of the electron theory was made by J. J. Thomson, who concluded that "for each valency bond established between two atoms the transference of one (negatively charged) corpuscle from one atom to the other has taken place, the atom receiving the corpuscle acquiring a unit negative charge." *

Stieglitz,† Falk and Nelson,‡ L. W. Jones,§ Fry,‖ W. A. Noyes,¶ Eastman** and others have contributed to the development of the theory. They have applied it to many of the principal types of chemical reactions, using it as a basis for classification of reactions, including oxidation and reduction processes, intramolecular rearrangements, and as a basis for predicting the results of substitution and addition in many

* Thomson, The Corpuscular Theory of Matter, p. 138 (1907).

† Stieglitz, *J. Am. Chem. Soc.*, **44**, 1293 (1922).

‡ Falk and Nelson, *J. Am. Chem. Soc.*, **32**, 1637 (1910). Ibid., **36**, 209 (1914).

§ L. W. Jones, *Am. Chem. J.*, **50**, 414 (1914).

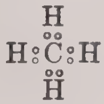
‖ Fry, *J. Am. Chem. Soc.*, **39**, 1688 (1917).

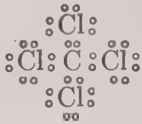
¶ W. A. Noyes, *Science*, **49**, 175 (1919).

** Eastman, *J. Am. Chem. Soc.*, **44**, 438 (1922).

types of compounds. Some of these applications will be considered in later chapters.

The arbitrary distribution of electrons in the outer shells of atoms as indicated above (p.11) may be used to indicate molecular and ionic structures. The formulas for methane and carbon tetrachloride may be written as follows:





Each hydrogen has its pair of electrons while the carbon and chlorine atoms have complete octets. A valence bond consists of a pair of electrons occupying a stable position between two atoms. In strictly non-polar compounds, if such exist, each electron of the pair belongs as much to one as to the other of the elements so bound. If there is a great difference in the tendencies of the united elements to hold or to yield electrons, we have a polar compound, capable of ionization. In the absence of strong preferential tendencies to acquire or give up the charge, we have the typical non-polar, inert, organic compounds. A double bond is represented by two pairs of electrons between the elements so united, and since it is impossible for each of two pairs to occupy the position of maximum stability the molecule is distorted. Enhanced activity of the molecule is, therefore, to be expected when, by any process, a double bond is established.

This theory is in substantial accord with the view expressed recently by J. J. Thomson. His work on electrical discharges through gases has compelled him to give up his earlier belief in the complete transfer of an electron from one atom to another, and he says we must now conclude that the electrical force which holds atoms together in molecules is due "not to one atom being charged positively and the other negatively, but to the displacement of positive and negative electricity in each atom."*

APPLICATIONS

It may be well to offer at this point one or two illustrations of the use of the electron theory in reactions with which the student is already familiar.

* Thomson, *Phil. Mag.*, 24, 249 (1912).

Combination. Hydrogen and chlorine unite by coming into such relation as is necessary to complete a pair of electrons for hydrogen and an octet for chlorine.

$$\mathrm{H}\circ + \circ\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon \longrightarrow \mathrm{H}\colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon.$$

Atoms of elementary gases combine to form molecules, not on account of electrical differences between them, but to establish the stable state which is dependent upon the completion of an octet of electrons around each atom. Thus, two chlorine atoms combine to form Cl_2 as follows:

$$\colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\circ + \circ\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon \longrightarrow \colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon.$$

Dissociation. Thermal dissociation of a gas results in the formation of the original, electrically neutral atoms, as represented by a reversal of the above equation; but in such cases as referred to by Noyes * and by Stieglitz †, where reactions evidently require positive and negative chlorine atoms, we must assume that the dissociation is influenced by the environment in such a way as to leave six electrons on one atom and eight on the other.

$$\colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon \longrightarrow \colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}^{+} \text{ and } \colon\!\underset{\circ\circ}{\overset{\circ\circ}{\mathrm{Cl}}}\!\colon^{-}.$$

In polar compounds the valence pair of electrons is drawn closer to the negative than to the positive atom and in ionizing solvents such atoms have a tendency to drift apart, the negative ion carrying both electrons of the valence pair.

Oxidation and Reduction. Oxidation is accompanied by, or is the result of, a change of valence. It is defined as the change in the state of an element which is brought about by the loss of one or more electrons. Reduction is the result of acquiring electrons. ‡ It is, in a strict sense, incorrect to speak of the oxidation of ferrous chloride to ferric chloride by the action of potassium dichromate. The ferrous ion, Fe^{++}, is the thing that is oxidized by yielding to the oxidizing agent, one electron, thereby forming the ferric ion Fe^{+++}. And it is not potassium dichromate which is the actual oxidizing agent

* Noyes, *J. Am. Chem. Soc.*, **23**, 460 (1901).

† Stieglitz, *J. Am. Chem. Soc.*, **23**, 1796 (1901).

‡ Nelson, Beans, and Falk, *J. Am. Chem. Soc.*, **35**, 1810 (1913).

nor is it the oxygen of the compound; but it is the dichromate ion $Cr_2O_7^{--}$ in which the chromium atom suffers reduction from Cr^{++++++}, as it exists in the dichromate ion, to Cr^{+++}, as it appears at the end of the reaction in the chromic ion. Since the number of atoms of electricity, as well as all others, must remain unchanged in any reaction, this affords the most convenient means of balancing an equation.* Each iron atom loses one electron; each chromium atom acquires three. Since no other oxidation or reduction process is involved, we know that three iron atoms are reduced by each chromium atom, or six iron atoms by the chromium contained in each molecule of potassium dichromate. The valence † of chromium in $K_2Cr_2O_7$ is $+6$; and in chromic chloride it is $+3$. Iron in ferrous chloride has a valence of $+2$, and in ferric chloride $+3$. We have, therefore,

$$K_2Cr_2O_7 + FeCl_2 + HCl \longrightarrow FeCl_3 + CrCl_3 + KCl + H_2O.$$

Fe lost 1 electron

Each Cr gained 3; total 6

Then six molecules of ferrous chloride to one of potassium dichromate must be taken.

$$K_2Cr_2O_7 + 6FeCl_2 + HCl \longrightarrow 2CrCl_3 + 6FeCl_3 + 2KCl + H_2O.$$

To account for the number of chloride ions now appearing on the right side of the equation and also to provide hydrogen enough for the seven atoms of oxygen on the left side, it is obvious that fourteen molecules of hydrochloric acid must be used.

$$K_2Cr_2O_7 + 6FeCl_2 + 14HCl \longrightarrow 2CrCl_3 + 6FeCl_3 + 2KCl + 7H_2O.$$

We are in no way concerned with the potassium ions; they could just as well be sodium or ammonium; nor is there anything in the reaction that is dependent upon chloride ions. The ionic equation is simpler and it more accurately represents the changes taking place.

* Hildebrand, Principles of Chemistry, pp. 226–233.

† The valence of oxygen is always -2 and of potassium $+1$. The number of plus and minus charges in any neutral molecule must be equal. We have then $7 \times -2 = -14$ for oxygen and $2 \times +1$ for potassium, leaving 12 charges to be divided between the two chromium atoms. In the chromic chloride formed we have $3 \times -1 = -3$ for the chlorine and hence the one chromium atom in the molecule has a valence of $+3$.

$$Cr_2O_7^{--} + Fe^{++} + H^+ \longrightarrow Fe^{+++} + Cr^{+++} + H_2O.$$

Fe lost 1 electron

Each Cr gained 3; total 6

then

$$Cr_2O_7^{--} + 6Fe^{++} + 14H^+ \longrightarrow 2Cr^{+++} + 6Fe^{+++} + 7H_2O.$$

The same principles apply to organic reactions. Thus, acetaldehyde, $CH_3 \cdot CHO$, is oxidized to acetic acid, $CH_3 \cdot COOH$, by an acid solution of a permanganate. The CH_3 group appears in the acid, as well as in the aldehyde, and has not been changed in any way. We may disregard it entirely or we may assign to it the same valence (+1) in both cases,

$$H^+ + MnO_4^- + CH_3 \cdot CHO \longrightarrow CH_3 \cdot COOH + Mn^{++} + H_2O.$$

0 to + 2

Valence change + 7 to + 2

Each manganese atom acquires five electrons. One carbon in each aldehyde molecule gives up two. It will take, therefore, two permanganate ions to oxidize five aldehyde molecules, and to balance the equation we must add hydrogen ions (acid) enough to make the electrical charges equal on the two sides of the equation.

$$6H^+ + 2MnO_4^{--} + 5CH_3 \cdot CHO \longrightarrow 5CH_3 \cdot COOH + 2Mn^{++} + 3H_2O.$$

As another example let us consider the reaction between formaldehyde and ammonia. The products of the reaction are trimethylamine, $(CH_3)_3N$, water, and carbon dioxide.

$$CH_2O + NH_3 \longrightarrow (CH_3)_3N + CO_2 + H_2O.$$

No change in the valence of nitrogen is produced. In formaldehyde, CH_2O, we may regard the polar valence of carbon as 0. Its actual valence, as measured by the bonds between the carbon atom and the other atoms, is four, but there are as many positive as negative charges on the atom. In the reaction indicated above some of the carbon atoms are oxidized to carbon dioxide and others are reduced to the state represented in the formula for trimethylamine.

$$CH_2O + NH_3 \longrightarrow (CH_3)_3N + CO_2 + H_2O.$$

0 to − 2

Valence change 0 to + 4

For each carbon atom oxidized to CO_2 there must be two carbon atoms reduced to the trimethylamine stage, for the oxidation involves a loss of four electrons and the reduction an acquisition of only two electrons on each carbon atom undergoing a change of state. There are three carbon atoms in the trimethylamine molecule, each of which has gained two electrons — a total of six. The one carbon in CO_2 has lost four electrons. The production of one mol of the amine must be accompanied by the formation of six fourths, or one and one half mols of carbon dioxide. Expressing this ratio in the smallest possible whole numbers, we have:

$$CH_2O + NH_3 \longrightarrow 2(CH_3)_3N + 3CO_2 + H_2O.$$

To obtain nine carbon atoms and two nitrogen atoms as now indicated in the products of the reaction, we must use nine mols of formaldehyde and two of ammonia. The equation then becomes

$$9CH_2O + 2NH_3 \longrightarrow 2(CH_3)_3N + 3CO_2 + 3H_2O.^*$$

Throughout this text we will use the term *valence* as a measure of the number of electrons an atom may yield or receive in the formation of a stable compound, or the number of pairs of electrons it may share with other atoms. We will, however, retain the established custom of indicating a chemical bond by either a line or a dot, except in reactions that are best explained by considerations of electron displacements.

* In practice a solution of ammonium chloride in formalin (40 per cent formaldehyde) is used. The amine is formed when the solution is heated to 120° in an autoclave or in a sealed tube (Koeppen, *Ber.*, 38, 882). An improved procedure is outlined by Adams and Conant (Organic Syntheses, Vol. I, Wiley and Sons). Ammonium chloride is mixed with paraformaldehyde and heated under a reflux condenser at atmospheric pressure. For the reaction between formaldehyde and ammonia in aqueous solution at ordinary temperatures see page 82.

ALIPHATIC COMPOUNDS

HYDROCARBONS

The Methane Series

The hydrocarbons are compounds composed of hydrogen and carbon only. They constitute the simplest types of carbon compounds and from them all others may be derived; but in many cases the processes involved in making other classes of compounds from hydrocarbons are not simple nor direct.

The hydrocarbons are classified as saturated or unsaturated on the basis of their tendencies to form substitution or addition products. Chlorine, for example, may react with a hydrocarbon by addition, forming a compound which contains a definite amount of chlorine in addition to all of the carbon and hydrogen of the original molecule; with other hydrocarbon molecules chlorine may react only by replacing an equivalent amount of hydrogen, chlorine atoms being substituted for hydrogen atoms. Compounds that form addition products are unsaturated; those that form substitution products only are saturated.

The saturated hydrocarbons are closely related to each other in chemical composition and molecular structure. The simplest member of the group is methane, CH_4, commonly called marsh gas, and the entire group is known as the methane series. The group is referred to also as the paraffin series or the saturated series. Physical constants of a few normal members are given in the table on opposite page.

The first four members of the series are arbitrarily named methane, ethane, propane, and butane. The name of each higher member is derived from the Greek numeral corresponding to the number of carbon atoms in the molecule. It will be observed that the members of the series differ from each other in composition and molecular weight by CH_2 or n times CH_2. They correspond to the general formula C_nH_{2n+2}. They constitute a homologous series, that is, a series of compounds so related that when arranged in the order of increasing

PARAFFIN HYDROCARBONS

Name	Formula	Melting Point	Boiling Point	Specific Gravity
Methane . . .	CH_4	–186°	–160°	0.415 (at –160°)
Ethane . . .	C_2H_6	–172°	–93°	0.446 (at 0°)
Propane . . .	C_3H_8	–189.9°	–45°	0.536 (at 0°)
Butane . . .	C_4H_{10}	–135°	1°	0.600 (at 0°)
Pentane . . .	C_5H_{12}	–130.8°	36.3°	0.627 (at 14°)
Hexane . . .	C_6H_{14}	–94°	68.9°	0.658 (at 20°)
Heptane . . .	C_7H_{16}	–97°	98.4°	0.683 (at 20°)
Octane . . .	C_8H_{18}	–57.4°	125.6°	0.702 (at 20°)
Nonane . . .	C_9H_{20}	–51°	149.5°	0.718 (at 20°)
Decane . . .	$C_{10}H_{22}$	–31°	173°	0.730 (at 20°)
Undecane . . .	$C_{11}H_{24}$	–26°	194°	0.774 (at m.p.)
Dodecane . . .	$C_{12}H_{26}$	–12°	214.5°	0.773 (at m.p.)
Tetradecane . .	$C_{14}H_{30}$	4°	252.5°	0.775 (at m.p.)
Hexadecane . .	$C_{16}H_{34}$	18°	287.5°	0.775 (at m.p.)
Eicosane . . .	$C_{20}H_{42}$	36.5°	205°*	0.777 (at m.p.)
Heneicosane . .	$C_{21}H_{44}$	40.1°	215°*	0.778 (at m.p.)
Tricosane . . .	$C_{23}H_{48}$	47.4°	234°*	0.779
Hentriacontane .	$C_{31}H_{64}$	68.4°	302°*	0.780
Hexacontane . .	$C_{60}H_{122}$	101°		

* At 15 mm. pressure.

molecular weights there is a constant difference in composition between successive members.

Properties. The saturated hydrocarbons are inert, unreactive, and very stable. The first four members (C_1 to C_4) are gases at ordinary temperatures and pressures. The next twelve members (C_5 to C_{16}) are liquids, and those of still higher molecular weight are solids. The melting points and boiling points become higher as the molecular weights increase. The densities increase in the same order but never exceed the density of water. They are all practically insoluble in water but completely miscible in each other. The gases are odorless, the liquids have odors resembling petroleum, which is a mixture of all of them, and the solids are odorless. All are colorless. The liquid members have a burning taste; the higher members are tasteless.

The saturated hydrocarbons are attacked very slowly or not at all by the ordinary reagents of the laboratory. Potassium permanganate solution has practically no effect upon the normal straight-chain compounds but does oxidize many of the branched-chain molecules, especially those having hydrogen attached to a tertiary carbon atom (a carbon atom linked to

three other carbon atoms). Such molecules are quite susceptible to oxidation; they yield carbon dioxide, water, and acids of low molecular weight.

Concentrated sulphuric acid combines with the higher paraffins, forming sulphonic acids.* The liquid members are more or less soluble in sulphuric acid but they are released unchanged when the acid is diluted with water. Hydrochloric acid does not react with any of the paraffins. They are unaffected also by sodium and potassium hydroxides.

Cold dilute nitric acid does not oxidize nor nitrate the saturated hydrocarbons; but the concentrated acid acts slowly upon normal paraffins, and more rapidly upon those having hydrogen attached to tertiary carbon, replacing hydrogen by the NO_2 group with the elimination of water. This reaction is never a smooth one, however; only a small quantity of the nitro-compound is formed and it is invariably mixed with oxidation products. Hot dilute nitric acid produces somewhat similar results.

In direct sunlight a mixture of methane and chlorine may explode with the formation of hydrogen chloride and deposition of free carbon:

$$CH_4 + 2Cl_2 = 4HCl + C.$$

With bromine this reaction does not occur, but fluorine and methane explode when mixed, even in the dark and at low temperatures. Iodine fails to react with any saturated hydrocarbon. In diffused light at low temperatures, and more rapidly as the temperature is raised or the intensity of the light is increased, chlorine and bromine act upon the hydrocarbons, producing substitution products. The action of chlorine on methane is typical and may be represented by the following equations:

$$CH_4 + Cl_2 \longrightarrow \underset{\text{Methyl chloride}}{CH_3Cl} + HCl;$$

$$CH_3Cl + Cl_2 \longrightarrow \underset{\text{Methylene chloride}}{CH_2Cl_2} + HCl;$$

$$CH_2Cl_2 + Cl_2 \longrightarrow \underset{\text{Chloroform}}{CHCl_3} + HCl;$$

$$CHCl_3 + Cl_2 \longrightarrow \underset{\text{Carbon tetrachloride}}{CCl_4} + HCl.$$

* Worstall, *J. Am. Chem. Soc.*, **20**, 245 (1899).

It is not possible to secure either of these products in a pure state by the direct action of chlorine on methane. A mixture is always obtained, for the reactions proceed simultaneously and before all of the methane has been converted into methyl chloride a part of it has reached the stage represented in the last equation.

The homologues of methane react with chlorine and bromine in the same way, except that the reaction becomes slower with increasing molecular weight and it is not possible to remove all of the hydrogen by direct substitution in compounds containing more than three carbon atoms.

Alkyl radicals. Many different types of compounds may be derived from a saturated hydrocarbon by substituting for hydrogen another element or a group of elements. Thus, from methane we obtain methyl chloride, CH_3Cl; methyl alcohol, CH_3OH; methyl cyanide, $CH_3 \cdot CN$; and acetic acid, $CH_3 \cdot COOH$. The corresponding derivatives of ethane are ethyl chloride, C_2H_5Cl; ethyl alcohol, C_2H_5OH; ethyl cyanide, $C_2H_5 \cdot CN$; and propionic acid, $C_2H_5 \cdot COOH$.

In all these compounds the univalent groups $CH_3—$ and $C_2H_5—$ will be recognized as derivatives of the hydrocarbons CH_4 and C_2H_6. These univalent groups derived from aliphatic hydrocarbons by the removal of one hydrogen atom are called *alkyl* radicals. They do not exist independently. They occur only in combination with other elements or groups. An alkyl radical is named from the hydrocarbon having the same number of carbon atoms, the termination *ane* being changed to *yl*. Thus $CH_3—$ is methyl, $C_2H_5—$ ethyl, C_3H_7 propyl, $C_4H_9—$ butyl, and so on. The letter R will be used as a symbol for any alkyl radical and X will be written as a symbol for any halogen. It will be convenient at times to use general formulas representing classes of compounds instead of specific formulas representing individual members of a class. Thus, the formula RI may be used for any alkyl radical combined with iodine and RX is a general formula for any alkyl radical in combination with any halogen atom.

Methane. CH_4 is a colorless, odorless gas. It burns with a pale blue flame, forming carbon dioxide and water. Only 5.4 cc. of the gas will dissolve in 100 cc. of water at 0°. Its solubility in alcohol is 52.2 cc. per 100 cc. of the solvent. It forms an explosive mixture with air and has caused many

disastrous explosions in coal mines, where it issues from the crevices in the coal seams. The miners call it "fire-damp." Methane is a component of the gases escaping from petroleum and natural gas wells. It is formed wherever vegetable matter decays under water and it constitutes the chief component of marsh gas. It is produced in large quantities in the distillation of coal. The coal gas manufactured for heating and lighting purposes is from 30 to 40 per cent methane. Methane boils at $-160°$ and solidifies at $-186°$. Its critical temperature is $-82°$ and its critical pressure fifty-five atmospheres.

Preparation. Methane may be obtained by the following methods:

1. By distilling dry sodium acetate with soda lime (a mixture of sodium hydroxide and lime):

$$CH_3COONa + NaOH \longrightarrow CH_4 + Na_2CO_3.$$

2. By the action of water on methyl magnesium iodide:

$$CH_3 \cdot MgI + HOH \longrightarrow CH_4 + MgIOH.$$

3. By heating to 300° C. a mixture of carbon monoxide or carbon dioxide and hydrogen in the presence of finely divided nickel:

$$CO + 3H_2 \longrightarrow CH_4 + H_2O;$$
$$CO_2 + 4H_2 \longrightarrow CH_4 + 2H_2O.$$

4. By direct union of carbon and hydrogen. Dry hydrogen gas is passed through a tube containing finely divided carbon and nickel. At 475° C. and one atmosphere of pressure the equilibrium established corresponds to 51 per cent methane and 49 per cent hydrogen.

GENERAL METHODS FOR PREPARING HYDROCARBONS

The first and second methods listed for the preparation of methane are applications of general reactions.

1. The sodium salt of an acid when distilled with soda lime yields a hydrocarbon with one less carbon atom than was present in the acid. Sodium acetate, CH_3COONa, was used to make methane. To prepare ethane by this method a salt of propionic acid, C_2H_5COOH, must be used:

$$C_2H_5COONa + NaOH \longrightarrow C_2H_6 + Na_2CO_3.$$

The method applies to the formation of all the gaseous and liquid hydrocarbons of the saturated series.

2. An alkyl magnesium halide on hydrolysis yields a hydrocarbon. The reagent is prepared by dissolving metallic magnesium in an ether solution of an alkyl chloride, bromide, or iodide. To prepare propane by this method propyl magnesium halide is employed:

$$C_3H_7MgBr + HOH \longrightarrow C_3H_8 + MgOHBr.$$

3. A method devised by Wurtz for building up the higher members from those of lower molecular weight consists of removing halogen atoms from alkyl halides by means of zinc or sodium. The metallic halide is formed and the alkyl radicals unite to form hydrocarbons. For example, chlorine is removed from methyl chloride and the methyl groups combine in pairs to form ethane:

$$\begin{matrix} CH_3Cl \\ \\ CH_3Cl \end{matrix} + 2Na \longrightarrow 2NaCl + \begin{matrix} CH_3 \\ | \\ CH_3 \end{matrix}.$$

A mixture of ethyl chloride and methyl chloride with sodium yields the next higher member, propane:

$$\begin{matrix} C_2H_5Cl \\ \\ CH_3Cl \end{matrix} + 2Na \longrightarrow 2NaCl + \begin{matrix} C_2H_5 \\ | \\ CH_3 \end{matrix}.$$

In this case ethane would be produced at the same time from pairs of methyl groups and butane from the union of ethyl radicals. The mixed gases are not easily separated and the method is not a practical one on that account. It is, however, a reaction of great theoretical interest, for it establishes a genetic relationship between the different hydrocarbons.

STRUCTURE AND ISOMERISM

Compounds having the same composition and the same molecular weight, but differing in properties, are called isomers. The structure theory accounts for this phenomenon. There can be but one compound with the formula CH_4. Its structure is represented by the formula

$$\begin{matrix} & H & \\ & | & \\ H- & C & -H. \\ & | & \\ & H & \end{matrix}$$

The four valences of carbon are equal and the hydrogen atoms are symmetrically placed with reference to the carbon. A rigid proof of these postulates cannot be made until familiarity with the general reactions of organic chemistry has been acquired. There is ample evidence in support of the supposition that the valences of the carbon atom are exercised at points corresponding to the apexes of a tetrahedron. Ethane is derived from methane by the replacement of one of the four similarly placed hydrogen atoms by CH_3. It makes no difference which hydrogen is replaced; only one structure is possible for the resulting compound, namely:

$$\begin{array}{ccccccc} & & H & & H & & \\ & & | & & | & & \\ H & — & C & — & C & — & H \\ & & | & & | & & \\ & & H & & H & & \end{array}$$

This structural formula of ethane is a projection on one plane of a three-dimensional body, supposed to be made up of two tetrahedral carbon atoms attached at one apex of each and holding one hydrogen atom at each of the other six points. Obviously, the six hydrogen atoms in ethane are similarly placed. Each bears the same relation to the molecule as does any other. Substituting a methyl group for one of these hydrogen atoms gives propane:

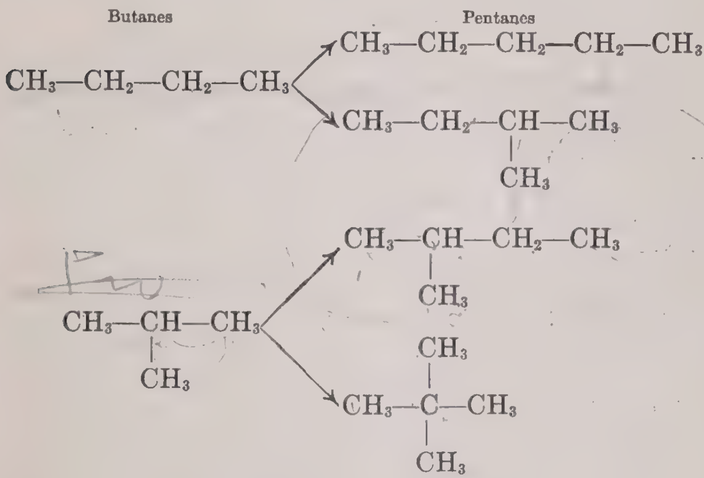
$$\begin{array}{ccccccccc} & & H & & H & & H & & \\ & & | & & | & & | & & \\ H & — & C & — & C & — & C & — & H \\ & & | & & | & & | & & \\ & & H & & H & & H & & \end{array} \qquad \text{or} \qquad CH_3—CH_2—CH_3$$

The same process of substitution applied to propane yields butane. But the hydrogen atoms in propane are not all in similar positions. Six of them are in like positions on terminal carbon atoms. Two of them occupy like positions (but different from the other six) on the central carbon atom. Substituting CH_3 for one of the terminal hydrogen atoms in $CH_3—CH_2—CH_3$ produces a butane, C_4H_{10}, having the structure $CH_3—CH_2—CH_2—CH_3$. Replacing one of the central hydrogen atoms by CH_3 would yield a molecule, C_4H_{10}, having the structure

$$\begin{array}{ccccc} CH_3 & — & CH & — & CH_3 \\ & & | & & \\ & & CH_3 & & \end{array}$$

According to the structure theory, then, there should be two different compounds having the formula C_4H_{10}. Two butanes are actually known. Normal butane, the compound having a straight chain of carbon atoms, boils at 1° C., and *iso*butane, the branched-chain compound, boils at 17° C.

All possible structures for the pentanes may be derived in the same way from the butanes:



(1) (2) (3) (4)

Apparently there should be four pentanes, but close inspection reveals the fact that formulas (2) and (3) are identical structures. The number is therefore reduced to three. Three, and only three, pentanes are known. They are liquids boiling at 36°, 30°, and 9° C., respectively.

The possible structures increase in number rapidly as the number of atoms in the molecule increases. There are five hexanes, nine heptanes, eighteen octanes, thirty-five nonanes, seventy-five decanes, and so on. Not all of these possible structures have been built up, for chemists have had more important tasks to perform; but the methods for synthesizing a compound of any given structure have been developed and could, no doubt, be applied in all these cases.

Nomenclature. The existence of isomers renders inadequate the system of nomenclature outlined above (p. 18). The plan commonly employed is that of naming every paraffin hydrocarbon as a derivative of methane. Just as CH_3Cl, CH_2Cl_2,

and $CHCl_2Br$ would be called chlor-methane, dichlor-methane, and brom-dichlor-methane, respectively, so the three pentanes;

$$1.\ CH_3{-}CH_2{-}\overset{*}{C}H_2{-}CH_2{-}CH_3;$$

$$2.\ \begin{array}{l}CH_3\diagdown\\ \\ CH_3\diagup\end{array}\!\!\overset{*}{C}H{-}CH_2{-}CH_3;$$

$$3.\ \begin{array}{l}CH_3\diagdown\\ \\ CH_3\diagup\end{array}\!\!\overset{*}{C}\!\!\begin{array}{l}\diagup CH_3\\ \\ \diagdown CH_3\end{array}.$$

may be named (1) diethyl-methane, (2) dimethyl-ethyl-methane, and (3) tetramethyl-methane. The atoms marked * are the methane carbon atoms in the structures corresponding to these names. Any carbon atom in the molecule may be chosen as representing the methane residue, and several different names might be applied to the same compound. This, however, causes no confusion, for, while a single compound might be known by different names, two different compounds cannot have the same name. If, in each of the examples just given, we select the next carbon atom to the right of the one marked * as being the methane carbon, the names become (1) methyl-propyl-methane, (2) methyl-isopropyl-methane, and (3) tertiarybutyl-methane. The isomeric forms of the alkyl radicals are distinguished by appropriate names. The propyl group, C_3H_7—, may be $CH_3{-}CH_2{-}CH_2{-}$ or

$$\begin{array}{l}CH_3\diagdown\\ \\ CH_3\diagup\end{array}\!\!CH{-}$$

The first is normal propyl and the second *iso*propyl. The butyl radical, C_4H_9—, may have the structures

$$(1)\ CH_3{-}CH_2{-}CH_2{-}CH_2{-},$$

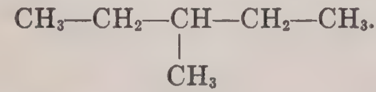
$$(2)\ \begin{array}{l}CH_3\diagdown\\ \\ CH_3\diagup\end{array}\!\!CH{-}CH_2,\quad (3)\ \begin{array}{l}CH_3\diagdown\\ CH_3{-}\\ CH_3\diagup\end{array}\!\!C{-}.$$

The first is normal butyl (straight chain). The second is *iso*butyl (branching at the end of the chain as in *iso*propyl), and the third is tertiary butyl. The carbon having the free valence in (3) is a tertiary carbon atom, that is, it is linked to three other carbon atoms. A carbon atom, if linked to two

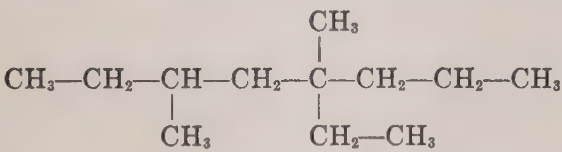
other carbon atoms, is called secondary and if attached to only one other is said to be a primary carbon atom.

The Geneva system. In the year 1892 an international congress of chemists assembled in Geneva to devise a uniform and scientific system of nomenclature for chemical compounds. The system developed by the Geneva Congress is used in many reference books and should be understood by all who intend to read chemical literature.

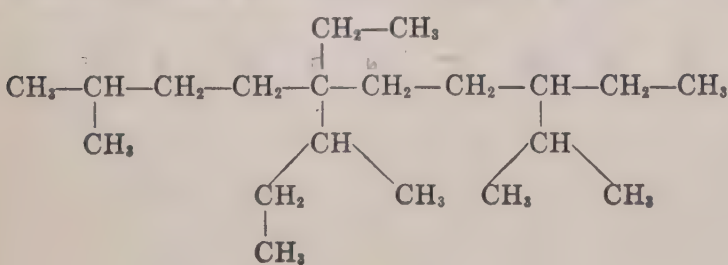
A hydrocarbon is named as a derivative of the normal compound corresponding to the longest continuous chain of carbon atoms in the molecule. For example, there are five carbon atoms in the longest continuous chain in the structure,



The compound is called 3-methyl-pentane. The numeral, 3, placed before the name indicates that the methyl group is attached to the third carbon atom in the pentane chain.



is 3-methyl-5-methyl-5-ethyl-octane. Positions in the side chains are indicated by using a prime or accent mark after the numeral, and if branching occurs in a side chain an additional accent mark is used in connection with each branch. The position of every carbon atom in the molecule is thus defined. A side chain is named as a derivative of the alkyl group corresponding to the longest straight chain in it and substituents in the alkyl radicals terminate in *o* instead of *yl*. Thus, ?



would be named 2-methyl-5-ethyl-5′-metho-5-propyl-8′-metho-8-ethyl-decane.

Petroleum. The chief natural source of the paraffin hydrocarbons is petroleum. The crude oil usually contains nearly all of the members of the series from CH_4 to $C_{27}H_{56}$. Unsaturated hydrocarbons, together with small quantities of compounds containing oxygen, nitrogen, and sulphur, are present also. The oil in some districts contains considerable quantities of naphthalene, anthracene, and asphaltum.

The origin of petroleum is unknown. Many theories have been advanced to account for the vast deposits, but no satisfactory explanation has yet been made. Mendelejeff believed the hydrocarbons were formed by the action of water on metallic carbides. His theory is unsatisfactory, for the composition of petroleum from all sources should be quite uniform if formed from water and metallic carbides. No uniformity exists. Pennsylvania oil is composed almost entirely of paraffin hydrocarbons. Oils from California, Texas, Oklahoma, and Kansas contain anthracene, naphthalene, and other benzene derivatives in addition to paraffins. Russian oils are rich in naphthalene and its homologues.

According to Engler petroleum was formed from the fat of animal tissues. But this theory, also, is unsatisfactory. It may, however, apply to California oil, which contains nitrogen and sulphur compounds and is obtained from regions that abound in remains of animals of recent geological periods and the fossils of sea and land animals of earlier times. A similar theory, based on the nature of the nitrogen compounds found in petroleum, has been advanced by Mabery.* Nitrogen and sulphur compounds are present in the flesh of all animals.

The production of petroleum was not limited to a single geological period. The Pennsylvania oils are in the Upper Silurian, California deposits in the Miocene, and the principal Russian deposits belong to the Tertiary Epoch.

The crude oil varies in color from greenish red to black (sp. gr. 0.76 to 0.98). By distillation it is separated into several fractions. The first fractions are gases or very light, low-boiling liquids, and the last fractions are waxlike solids. The following table includes some of the distillation products of a typical eastern oil:

* Mabery, *J. Am. Chem. Soc.*, **41**, 1690 (1919).

Substance	Boiling Point	Specific Gravity
Cymogene	0°–5°	0.58–0.60
Rhigoline	15°–20°	0.60–0.63
Petroleum ether	40°–65°	0.63–0.65
Gasoline	65°–80°	0.65–0.68
Ligroin	80°–120°	0.68–0.72
Benzine	120°–150°	0.72–0.75
Kerosene	150°–300°	0.75–0.86

Lubricating oils, paraffin wax, vaseline, and petrolatum are products of still higher boiling fractions. At high temperatures considerable "cracking" occurs, part of the oil, comprising compounds of high molecular weight, breaking up with the production of the lower members of the aliphatic and aromatic series and leaving a residue of coke.

The world's annual production of crude petroleum (1923) is approximately 550,000,000 barrels,* nearly 70 per cent of which is produced in the United States. Mexico furnishes about 12 per cent and Russia 8 per cent of the total supply. Within the United States the most productive regions are Oklahoma, California, Illinois, Texas, Ohio, West Virginia, and Pennsylvania.

Petroleum is classified as "paraffin-base" oil if the solid residue is rich in hydrocarbons of the paraffin or methane series. It is known as an "asphaltic-base" oil if in the heavier portions asphalt predominates. Asphalt is a black, solid, heterogeneous substance composed largely of polymers of aromatic and aliphatic hydrocarbons and some of their oxidation products. It usually contains sulphur and nitrogen compounds also. Asphalt is insoluble in water and in alcohol but dissolves readily in benzene, acetone, and carbon bisulphide. Paraffin and asphalt may be separated by extraction of the former with alcohol.

California oils belong to the asphaltic class. They contain thiophen, pyridin, quinolin, and terpenes, as well as benzene, toluene, naphthalene, anthracene, and xylene, in addition to paraffin hydrocarbons.

Shale. In many localities there are large deposits of soft brown or gray shale containing complex carbon compounds. At dull red heat the crushed rock yields its organic matter in the form of hydrocarbon gases, oils, ammonia, paraffin, and related products. The crude mixture is refined by distillation,

* Forty-two gallons in one barrel.

as in the case of petroleum. Hydrocarbon oils are not present as such in shale.* They are formed from more complex carbon compounds during the process of distillation. The yield of oil obtainable from shale varies from zero to ninety gallons per ton. The richest and most extensive deposits in the United States are in Colorado, Utah, Wyoming, and Montana.

The distillation of shale for fuel oil has been an established commercial industry in France and Scotland since 1850.

The Ethylene Series

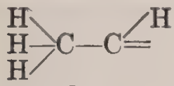
Ethylene, C_2H_4, a gas with a faint, sweet odor, was named by the early chemists olefiant (oil-forming) gas because it combines with chlorine and bromine, forming oily liquid products. Hydrocarbons derived from ethylene, corresponding in composition to the general formula C_nH_{2n}, are called olefins or alkylenes. The members of this series differ in many ways from the saturated hydrocarbons. They combine with chlorine and bromine by direct addition, forming halogen derivatives without loss of hydrogen. Each hydrocarbon in this series contains two less hydrogen atoms than the saturated hydrocarbon having the same number of carbon atoms. Theoretically the first member of the series should be methylene, CH_2, but this has never been isolated. The simplest known olefin is ethylene, C_2H_4.

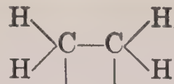
ETHYLENE HYDROCARBONS

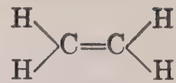
Name	Formula	Boiling Point
Ethylene	$CH_2{=}CH_2$	− 103°
Propylene	$CH_3{-}CH{=}CH_2$	− 49°
Butylene		− 5°
Ethylethylene	$C_2H_5{-}CH{=}CH_2$	
Sym. dimethylethylene	$CH_3{-}CH{=}CH{-}CH_3$	+ 1°
Isobutylene	$(CH_3)_2{-}C{=}CH_2$	− 6°
Amylene		
Normal propylethylene	$CH_3{-}CH_2{-}CH_2{-}CH{=}CH_2$	+ 40°
Isopropylethylene	$(CH_3)_2CH{-}CH{=}CH_2$	21°
Sym. methylethylethylene	$CH_3{-}CH{=}CH{-}C_2H_5$	36°
Unsym. methylethylethylene	$(CH_3)(C_2H_5)C{=}CH_2$	32°
Trimethylethylene	$(CH_3)_2{-}C{=}CH{-}CH_3$	36°
Hexylene (normal)	$C_4H_9{-}CH{=}CH_2$	70°
Heptylene (normal)	$C_5H_{11}{-}CH{=}CH_2$	72°
Octylene (normal)	$C_6H_{13}{-}CH{=}CH_2$	123°
Decylene (normal)	$C_8H_{17}{-}CH{=}CH_2$	172°

* McKee and Lyder, *J. Ind. Eng. Chem.*, **13**, 613 (1921).

There are three possible structures for ethylene:


I


II


III

In formula I the unsaturated condition of the molecule is represented by two free valence electrons on the same carbon atom. Such a compound would be a bivalent free radical and its addition product with chlorine would be $CH_3 \cdot CHCl_2$, both chlorine atoms being attached to the same carbon atom. Now, by the action of phosphorus pentachloride on acetaldehyde, $CH_3 \cdot CHO$, the oxygen of the aldehyde is replaced by two chlorine atoms, yielding a product with this structure. It bears very little resemblance to the addition product formed from ethylene and chlorine. The latter, therefore, must have one chlorine atom attached to each of the two carbon atoms and formula I must be abandoned. Formula II represents each carbon atom as trivalent. If carbon can exist in stable compounds in the trivalent state, or with a single free bond, there is no logical explanation for the fact that whenever an unsaturated compound forms an addition product with hydrogen or a halogen or with any other reagent it does so by combining with two atoms of hydrogen or halogen or, in general, with two equivalents of the atoms or ions of the reagent used. Since addition always involves a pair of atoms, ions, or radicals, we must assume that unsaturation is not due to single, isolated valence electrons nor to trivalent carbon, hence formula II is unsatisfactory. Formula III represents two carbon atoms linked to each other by a double bond, two of the four valences on each carbon atom being exercised in holding carbon to carbon. The activity of such a molecule is attributed to the strain involved in bringing the relatively fixed valence positions near enough together to admit of such a union. Addition of a halogen is interpreted, on the basis of this formula, as due to a breaking of the double bond, thereby allowing each of the carbon atoms to hold a halogen atom and thus forming a saturated compound. The structure of the chlorine addition product formed with ethylene then becomes $CH_2Cl \cdot CH_2Cl$, a structure that is in harmony with all known methods for its preparation.

Ethylene was made in large quantities during the war of 1914–1918. It was used in the manufacture of the very poisonous β-β-dichlor-ethyl

sulphide, commonly called mustard gas. The compound is an oily liquid (b.p. 216°; f.p. 14°). Its vapor, when inhaled, acts as a slow but certain poison. It penetrates the skin also and produces serious burns. It is formed by passing ethylene gas into a solution of sulphur dichloride in carbon tetrachloride:

$$S\begin{matrix}\diagup Cl \\ \diagdown Cl\end{matrix} + 2CH_2{:}CH_2 \longrightarrow S\begin{matrix}\diagup CH_2CH_2Cl \\ \diagdown CH_2CH_2Cl\end{matrix}$$

Unsaturated compounds are quite susceptible to oxidation. Ethane is not affected by chromic acid but ethylene is readily converted into carbon dioxide and water by this oxidizing agent. Energy is liberated when the double bond is broken. The heat of combustion of ethylene is greater than the heat of combustion of an equivalent quantity of free carbon and hydrogen, indicating a negative heat of formation for this hydrocarbon.

Preparation. Hydrocarbons of the ethylene series may be prepared by the following methods:

(1) An alkyl halide, when heated with an alcoholic solution of potassium hydroxide yields a molecule of hydrogen halide and an unsaturated hydrocarbon. The hydrogen and halogen are taken from adjacent carbon atoms and a double bond is thus established:

$$CH_3 \cdot CH_2 \cdot CH_2Cl + KOH \longrightarrow CH_3 \cdot CH : CH_2 + KCl + H_2O.$$

(2) Dihalogen derivatives of the paraffin hydrocarbons having the two halogen atoms attached to different, but adjacent, carbon atoms yield unsaturated hydrocarbons when warmed with zinc or sodium:

$$CH_3 \cdot CHCl \cdot CH_2Cl + Zn \longrightarrow CH_3 \cdot CH : CH_2 + ZnCl_2.$$

(3) Alcohols may be dehydrated by means of sulphuric acid or phosphorus pentoxide:

$$CH_3 \cdot CH_2 \cdot CH_2OH + H_2SO_4 \longrightarrow CH_3 \cdot CH : CH_2 + H_2SO_4 + H_2O.$$

Structural isomerism. Isomerism arises from changes in the configuration of the molecule either by branching of the carbon chains or by changing the position of the double bond. There are three possible structures for butylenes and three are actually known.

(1) $CH_3 \cdot CH : CH \cdot CH_3;$

(2) $CH_3 \cdot CH_2 \cdot CH : CH_2;$

(3) $\begin{matrix}CH_3\diagdown \\ CH_3\diagup\end{matrix} C : CH_2.$

The first (b.p. + 1°) is produced by the action of alcoholic potash on secondary butyl iodide, $CH_3 \cdot CHI \cdot CH_2 \cdot CH_3$, a little of (2) is simultaneously formed. The second (b.p. − 5°) is obtained in the same way from normal butyl iodide, $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2I$. The third is made by the action of sulphuric acid on isobutyl alcohol, $(CH_3)_2CH \cdot CH_2OH$.

Geometrical isomerism. Carbon atoms united by a single bond may rotate independently around their common axis, but a double bond between two atoms prevents free rotation. As a simple illustration of the principle involved in geometrical isomerism assume in one case that a single nail has been driven through two boards, as represented in Figure 2, I and II, and in another instance two nails have been driven through the boards, as shown in III and IV.

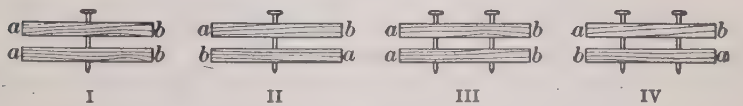


FIG. 2

In the first case either board may be turned around the nail so that corresponding ends (*aa* and *bb*) of the two may be placed on the same side (I) or on opposite sides (II) of the system. In the second case (III and IV) there is no such freedom. The boards are no longer able to rotate independently. If the corresponding ends (*aa*) were on the same side when the second nail was driven, they must remain there (III). If they were on opposite sides, they must remain as indicated in IV. Representing carbon atoms as tetrahedra, we may indicate the same principle as follows:

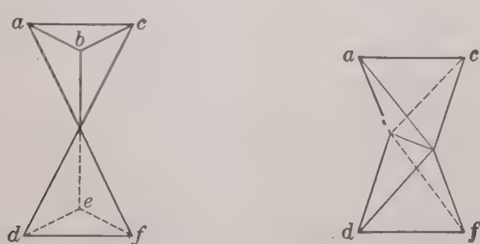


FIG. 3

The tetrahedra attached at one point only (Fig. 3, I) are free to rotate around their common axis so that *a* may be placed over *d*, *e*, or *f*, but tetrahedra attached to each other by two points (II) (having one edge in common) are not free to turn independently and hence the geometrical figure produced when the double bond is established cannot be altered without breaking the connection at one point or the other. A double bond thus gives rise to a new type of isomerism. To distinguish it from other types of structural variations in space it is called geometrical isomerism.

Due to the existence of the double bond, there are two brompropylenes corresponding to the formula $CH_3 \cdot CH : CHBr$. They are

$$\begin{array}{c} CH_3 \cdot C \cdot H \\ \| \\ H \cdot C \cdot Br \\ \text{Boiling point } 59.5° \end{array} \quad \text{and} \quad \begin{array}{c} CH_3 \cdot C \cdot H \\ \| \\ Br \cdot C \cdot H \\ \text{Boiling point } 66° \end{array}$$

Only a few of the pairs of ethylene hydrocarbons have been separated. More important examples of geometrical isomerism will be considered in connection with the study of unsaturated acids.

Nomenclature. The olefins are commonly named from the paraffin hydrocarbons having the same number of carbon atoms by changing the termination *ane* to *ylene*, thus, C_3H_6 is propylene, C_4H_8 butylene, C_5H_{10} amylene or pentylene. This system, however, is inadequate. It does not provide distinctive names for all isomers. They may be designated as derivatives of ethylene, just as the saturated hydrocarbons were named as derivatives of methane. Referring to the butylenes listed above, the names are (1) symmetrical dimethyl ethylene, (2) ethyl ethylene, (3) unsymmetrical dimethyl ethylene. According to the Geneva system they are named from the number of carbon atoms in the longest straight chain by changing the termination of the name of the corresponding paraffin from *ane* to *ene*. The position of the double bond is indicated by a number specifying the location of the first doubly linked carbon atom in the chain. Thus, $CH_2 : CH_2$ is ethene; $CH_3 \cdot CH : CH_2$ is propene; $CH_2 : CH \cdot CH_2 \cdot CH_3$ butene-1; $CH_3 \cdot CH : CH \cdot CH_3$ butene-2; and $\begin{matrix} CH_3 \\ CH_3 \end{matrix} \!\!> C : CH_2$ is 2-methyl-propene-2.

Addition compounds. Sulphuric, hydrobromic, hydriodic, hypobromous, and hypochlorous acids form addition products with the alkylenes. The halogens, nitric oxide, NO, and nitrogen peroxide, NO_2, also unite readily with these hydrocarbons. Among other reagents that break the double bond may be mentioned nitrosyl chloride, NOCl, chlorides of sulphur, SCl and SCl_2, hydrogen peroxide, ozone, and under some circumstances organic acids, acid chlorides, and water.

The following examples may be regarded as typical.

1. **Halogens.** Ethylene gas absorbs chlorine or bromine but not iodine:

$$CH_2 : CH_2 + Br_2 \longrightarrow \underset{\text{Ethylene dibromide}}{CH_2Br \cdot CH_2Br.}$$

Ethylene dibromide is a heavy, colorless liquid (sp. gr. 2.189, b.p. 131°) insoluble in water, soluble in alcohol and ether.

2. **Halogen Acids.** Hydrobromic and hydriodic acids combine with ethylene and its homologues. Hydrochloric acid fails to react in this way:

$$CH_2 : CH_2 + HI \longrightarrow \underset{\text{Ethyl iodide}}{CH_3 \cdot CH_2I.}$$

When polar compounds react with unsymmetrical derivatives of ethylene, the negative ion usually goes to the carbon atom which is holding the fewest hydrogen atoms. Hydrobromic acid, for example, combines with propylene as follows:

$$CH_3 \cdot CH : CH_2 + HBr \longrightarrow CH_3 \cdot CHBr \cdot CH_3.$$

Chlorine in hypochlorous acid has a positive valence and in reactions with unsymmetrical olefins its orientation follows the rule for positive and negative radicals given above:

$$CH_3 \cdot CH : CH_2 + ClOH \longrightarrow CH_3 \cdot CHOH \cdot CH_2Cl.$$

3. **Sulphuric Acid.** Ethylene dissolves in concentrated sulphuric acid with the formation of an alkyl sulphuric acid:

$$CH_2 : CH_2 + H_2SO_4 \longrightarrow CH_3 \cdot CH_2 \cdot SO_4H.$$

The ethyl sulphuric acid formed may be separated from unchanged sulphuric acid by precipitating the latter as barium sulphate. The barium salt of ethyl sulphuric acid is soluble. The soluble barium salt may then be treated with an equivalent quantity of sulphuric acid and the free ethyl sulphuric acid is obtained by vacuum distillation.

If the solution of an olefin in concentrated sulphuric acid is diluted with water and warmed, a saturated alcohol is produced:

$$CH_3 \cdot CH_2 \cdot HSO_4 + HOH \longrightarrow CH_3 \cdot CH_2OH + H_2SO_4.$$

4. **Oxidizing agents.** Permanganates and dichromates oxidize olefin hydrocarbons to dihydric alcohols (glycols). The reaction with permanganate ion in acid solution is represented by the equation,

$$5CH_2 : CH_2 + 2MnO_4^- + 6H^+ + 2H_2O \longrightarrow 5CH_2OH \cdot CH_2OH + 2Mn^{++}.$$

In alkaline solution a similar reaction occurs, but manganese dioxide instead of a manganous salt is formed.

$$3CH_2 : CH_2 + 2MnO_4^- + 4H_2O \longrightarrow 3CH_2OH \cdot CH_2OH + 2MnO_2 + 2OH^-$$

In this process, hydroxide ions are produced in a solution originally alkaline. If the reaction were reversible, we could predict that the process would be favored by the presence of an acid. But it is irreversible and it is catalyzed by hydroxide ions. An alkaline solution of a permanganate is, therefore, generally used to oxidize an unsaturated hydrocarbon.

5. **Reducing agents.** When the vapor of an unsaturated hydrocarbon is mixed with hydrogen gas and the mixture is passed over hot, finely divided nickel a saturated hydrocarbon is formed.

$$CH_2 : CH_2 + H_2 \longrightarrow CH_3 \cdot CH_3$$

The reduction of liquid and solid unsaturated hydrocarbons can be accomplished generally by treatment with concentrated hydriodic acid and red phosphorus.

The Acetylene Series

Unsaturated hydrocarbons corresponding to the general formula C_nH_{2n-2} may be divided into two classes: (1) compounds having one triple bond in each molecule and (2) those having two double bonds. To the first class belong acetylene, $HC \vdots CH$ and its homologues. The reasons for assigning to this formula a triple linkage between carbon atoms rather than assuming bivalent carbon or free-valence bonds are similar to those mentioned in the discussion of ethylene. Addition products are readily formed, univalent elements or groups

invariably adding in pairs. Bromine, for example, absorbs acetylene, forming dibromethylene and tetrabromethane.

$$HC{\equiv}CH + Br_2 \longrightarrow CHBr{=}CHBr;$$
$$CHBr{=}CHBr + Br_2 \longrightarrow CHBr_2{-}CHBr_2.$$

The reaction takes place in two stages and can be regulated by using an aqueous solution of bromine so as to yield the intermediate product, dibromethylene, CHBr : CHBr. The addition is catalyzed by light.

Acetylene is a colorless gas, almost insoluble in water but very soluble in acetone. At 15°, under one atmosphere of pressure one volume of acetone dissolves twenty-five volumes of the gas. The solubility increases rapidly as the pressure is increased or the temperature reduced. At −80° and 12 atmospheres of pressure the solubility is greater than 2000 : 1. Acetylene is an endothermic compound, the molecular heat of formation being −54 Cals. It decomposes, therefore, with a liberation of energy and when under two or more atmospheres of pressure it can be detonated by mercury fulminate or by an electric spark.

In an open container acetylene burns with a smoky flame but when used in a properly constructed burner, the flame is white, smokeless, and rich in rays of short wave length. The high temperature of the oxygen-acetylene flame gives the gas a technical value in welding processes. Iron is easily melted in the flame. Explosive mixtures of acetylene and air can be made with the proportions of the hydrocarbon varying from 3 per cent to 82 per cent, an unusually wide range. This property affords an explanation of the many explosions that have occurred in houses lighted by acetylene. Most other hydrocarbons, when mixed with air, burn quietly at the outlet if the air content of the mixture is below 50 per cent. The velocity of propagation of combustion is higher for acetylene than for other gases. This gives rise to a very sudden development of pressure and makes it unsafe to explode a mixture of acetylene and air even in an open flask.

The following reactions of acetylene are typical for members of this series:

1. Addition of halogens to form substituted olefins and saturated halogen compounds.

$$CH{\equiv}CH + Cl_2 \longrightarrow CHCl{=}CHCl;$$
$$CHCl{=}CHCl + Cl_2 \longrightarrow CHCl_2{-}CHCl_2.$$

2. Hydrogen bromide and hydrogen iodide slowly form derivatives of the olefins and finally unsymmetrical saturated dihalogen compounds:

$$CH{\equiv}CH + HBr \longrightarrow CH_2{=}CHBr;$$
$$CH_2{=}CHBr + HBr \longrightarrow CH_3{-}CHBr_2.$$

3. Hypochlorous and hypobromous acids combine with acetylene hydrocarbons, forming aldehydes:

$$CH \vdots CH + 2ClOH \longrightarrow CHCl_2 \cdot CH(OH)_2;$$
$$CHCl_2 \cdot CH(OH)_2 \longrightarrow CHCl_2 \cdot CHO + H_2O.$$

The addition product having two hydroxyl groups on the same carbon atom is unstable and cannot be isolated. Water is eliminated and a stable aldehyde is formed.

4. At low temperatures and under high pressure acetylene forms, with water, a crystalline hydrate $C_2H_2 \cdot 6H_2O$. Acetylene dissolves in concentrated sulphuric acid. When the acid is diluted with water and distilled, acetaldehyde is formed. The first reaction is an addition of sulphuric acid:

$$CH{\equiv}CH + 2H_2SO_4 \longrightarrow CH_3{-}CH(HSO_4)_2.$$

When heated with water this addition product decomposes, regenerating sulphuric acid and forming acetaldehyde:

$$CH_3{-}CH(HSO_4)_2 + H_2O \longrightarrow CH_3{-}CHO + 2H_2SO_4.$$

5. Nitric oxide and acetylene combine at high temperatures (800°) but the course of the reaction has not been fully determined. Water, carbon monoxide, nitrogen, and ammonium carbonate are among the products formed.

6. Hydrogen attached to a carbon atom which, in turn, is linked to another carbon by a triple bond may be replaced by metals. Silver acetylide is precipitated when acetylene gas is led into an ammoniacal solution of a silver salt. It is a white crystalline solid which explodes when agitated. Its formula is $Ag{-}C{\equiv}C{-}Ag$. Copper acetylide is a red explosive solid formed by passing acetylene gas into a solution of cuprous chloride in ammonia. The property of forming insoluble silver or copper derivatives distinguishes the compounds having the group $-C{\equiv}CH$ from all other hydrocarbons. Sodium and lithium carbides are formed when acetylene is passed into the molten metals. Free hydrogen or the hydride of the metal is simultaneously produced:

$$C_2H_2 + 2Na \longrightarrow C_2Na_2 + H_2;$$
$$C_2H_2 + 4Li \longrightarrow C_2Li_2 + 2LiH.$$

Similar compounds may be prepared by the direct action of carbon on many metals at temperatures attainable in the electric furnace.

Preparation. Acetylene is usually made by allowing water to drop on calcium carbide. The reaction is very energetic and must be carefully controlled to avoid excessive pressure in the generator:

$$CaC_2 + 2H_2O \longrightarrow Ca(OH)_2 + C_2H_2.$$

Calcium carbide is manufactured on a commercial scale by heating a mixture of lime and coke at 2500° to 3000° C. in an electric oven. Metallic calcium combines with carbon directly at a much lower temperature to form the same product; but a high temperature is required to reduce the calcium oxide. The mechanism of the process is indicated by two equations:

$$CaO + C \longrightarrow Ca + CO;$$
$$Ca + 2C \longrightarrow CaC_2.$$

Acetylene is formed from the free elements in an electric arc between carbon poles in an atmosphere of hydrogen. Equilibrium is attained (at 2500°) with less than 4 per cent of acetylene present. Traces of other hydrocarbons are formed at the same time.

Chloroform, bromoform, and iodoform yield their halogen atoms to molten sodium or potassium, the CH residues uniting in pairs to form acetylene:

$$2CHBr_3 + 6K \longrightarrow 6KBr + C_2H_2.$$

The higher members of the acetylene series are prepared by the following general methods.

1. Dihalogen derivatives of the saturated hydrocarbons having the two halogens attached to the same or to adjacent carbon atoms are treated with alcoholic potash.

$$CH_3{-}CH_2{-}CHCl_2 + 2KOH \longrightarrow CH_3{-}C{\equiv}CH + 2KCl + 2H_2O;$$
$$CH_3{-}CHCl{-}CH_2Cl + 2KOH \longrightarrow CH_3{-}C{\equiv}CH + 2KCl + 2H_2O.$$

2. Tetrahalogen compounds having two halogens attached to each of two adjacent carbon atoms yield acetylene derivatives when warmed with sodium or distilled with zinc dust.

$$CH_3{-}CCl_2{-}CHCl_2 + 2Zn \longrightarrow CH_3{-}C{\equiv}CH + 2ZnCl_2.$$

Nomenclature. Hydrocarbons containing triple bonds may be named as derivatives of acetylene. Thus $CH_3—C{\equiv}CH$ is methyl acetylene,

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH—C{\equiv}C—CH_2—CH_3,$$

is ethylisopropyl-acetylene, and so on. According to the Geneva plan the name is derived from the number of carbon atoms in the longest continuous chain. The name terminates in *ine* and the position of the triple bond is indicated by a number following the name. Thus,

$$\begin{array}{l} CH_3—CH—C{\equiv}C—CH_3 \\ \qquad\quad\ | \\ \qquad\ \ CH_3 \end{array}$$

is 2-methyl-pentine-3, or 4-methyl-pentine-2. The diolefine, $CH_2{=}C{=}CH_2$ is named propadiene;
$CH_2{=}CH—CH_2—CH{=}CH_2$ is pentadiene-1, 4, and
$CH{\equiv}C—CH_2—CH{=}CH_2$ is pentene-4-ine-1. The numeral, 4, refers to the position of the double bond, the presence of which is indicated by the ending *ene*, and the numeral, 1, refers to the position of the first carbon atom of the chain which is involved in the triple linkage indicated by the suffix *ine*.

DIOLEFINES

Hydrocarbons having two double bonds are isomeric with the acetylenes. Isoprene belongs to this group.

Isoprene is a liquid (b.p. 37°) obtained by distilling rubber or by passing turpentine vapor through a red-hot tube. Its structure is represented by the formula

$$\begin{array}{l} CH_2{=}C—CH{=}CH_2 \\ \qquad\ \ | \\ \qquad CH_3 \end{array}$$

Under the influence of concentrated hydrochloric acid isoprene polymerizes to a compound of unknown molecular weight apparently identical with rubber. Recent attempts to convert turpentine into rubber through the medium of isoprene have been more or less successful. It is a possibility of great promise.

THERMOCHEMICAL RELATIONS

The total energy change involved in passing from a definite initial to a definite final state is independent of the path. Hess

applied this principle to the calculation of heats of formation of organic compounds. Carbon dioxide, for example, may be formed directly from carbon and oxygen with the energy change indicated in the equation:

$$C + O_2 \longrightarrow CO_2 + 94{,}300 \text{ cals.}$$

One mol of carbon monoxide burns to carbon dioxide, as indicated in the equation:

$$CO + \tfrac{1}{2}O_2 \longrightarrow CO_2 + 68{,}100 \text{ cals.}$$

The difference between these values represents the energy change involved in forming one mol of carbon monoxide:

$$C + \tfrac{1}{2}O_2 \longrightarrow CO + 26{,}200 \text{ cals.}$$

By the same principle we may calculate the heats of formation of the hydrocarbons. Water and carbon dioxide are the products formed in the complete oxidation of a hydrocarbon; and we need, in addition to the data given above, the heat of formation of water:

$$H_2 + \tfrac{1}{2}O_2 \longrightarrow H_2O + 68{,}300 \text{ cals.}$$

The heat of formation of a substance represents the difference in energy content between one mol of the compound and an equal quantity of the uncombined elements. As a rule stable compounds are formed from the elements with an evolution of heat (loss of energy). But some compounds are formed with an absorption of energy. One mol of methane burns in oxygen, forming carbon dioxide and water with an evolution of 212,600 calories:

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O + 212{,}600 \text{ cals.} \qquad (1)$$

For the uncombined elements we have:

$$2H_2 + O_2 \longrightarrow 2H_2O + 136{,}600 \text{ cals.} \qquad (2)$$

$$C + O_2 \longrightarrow CO_2 + 94{,}300 \text{ cals.} \qquad (3)$$

Adding equations (2) and (3), we have:

$$2H_2 + C + 2O_2 \longrightarrow 2H_2O + CO_2 + 230{,}900 \text{ cals.} \qquad (4)$$

Subtracting (1) from (4):

$$2H_2 + C \longrightarrow CH_4 + 18{,}300 \text{ cals.}$$

This represents the energy used in breaking up the molecule when methane burns or it is the heat that would be evolved if methane were made by direct union of carbon and hydrogen.

On the other hand, some of the lower members of the unsaturated hydrocarbons burn with the evolution of more heat than is derived from equivalent weights of the free elements. In other words, they have negative heats of formation.

HEAT OF COMBUSTION

Methane	212,600 cals.	Ethylene	341,100 cals.
Ethane	372,300 cals.	Propylene	499,300 cals.
Propane	528,400 cals.	Butylene	650,200 cals.
Butane	687,200 cals.	Acetylene	310,900 cals.

ALCOHOLS

Saturated Monohydric Alcohols

The saturated monohydric alcohols may be regarded as derivatives of the paraffin hydrocarbons in which one hydrogen atom in each molecule has been replaced by a hydroxyl group. The general formula for alcohols of this series is $C_nH_{2n+1}OH$, or ROH. They may be prepared by the action of silver hydroxide on the alkyl halides. The iodides are generally employed.

$$C_2H_5I + AgOH \longrightarrow C_2H_5OH + AgI.$$

A hot aqueous solution of potassium hydroxide may be substituted for silver hydroxide, but the yield is poor in either case and these methods are of scientific interest only. The first two members of the series, methyl alcohol and ethyl alcohol, are of great commercial importance, and special means have been devised to produce them in vast quantities at comparatively low cost. These methods are outlined below.

Physical properties. The alcohols of low molecular weight are colorless liquids. The first three members of the series are miscible with water in all proportions. The members of the group containing from four to eleven carbon atoms are oily liquids sparingly soluble in water. The solubilities decrease as the molecular weights increase. The higher members are colorless solids, almost tasteless and odorless, and practically insoluble in water. They are readily soluble in the liquid members of the series and from these solutions some of them may be obtained in crystalline form.

Alcohols are classified as primary, secondary, and tertiary. The classification is based upon the number of carbon atoms that are bound by the carbon which is directly attached to the hydroxyl group. Every primary alcohol is characterized,

therefore, by the group $—CH_2OH$, while secondary and tertiary alcohols have the groups $—CHOH—$, and $\rangle COH$, respectively. General formulas may be written as follows:

$R \cdot CH_2OH$	R_2CHOH	R_3COH
Primary alcohol	Secondary alcohol	Tertiary alcohol

Chemical properties. 1. Alcohols react with metallic sodium or potassium with the evolution of hydrogen, but only one hydrogen atom in each molecule of a monohydric alcohol is replaceable by the metal. This fact is used in establishing the presence of a hydroxyl group in the alcohol molecule. For example, two structures are possible for a compound having the formula C_2H_6O. We might write it $CH_3 \cdot O \cdot CH_3$ or $CH_3 \cdot CH_2OH$. In the first formula the six hydrogen atoms are all similarly placed. If one is replaceable by a metal, there is no apparent reason why two, three, or even six, should not be replaced by the same reagent. In the second formula, five of the hydrogen atoms are attached directly to carbon and one is held by oxygen. The formula indicates that one hydrogen atom differs from all the others in its relation to the molecule as a whole, and since in ethyl alcohol, one and only one hydrogen atom is replaced by sodium, we assign to it the second formula and write the following equation for the reaction:

$$\underset{\text{Ethyl alcohol}}{CH_3 \cdot CH_2OH} + Na \longrightarrow \underset{\text{Sodium ethylate}}{CH_3 \cdot CH_2ONa} + \tfrac{1}{2}H_2.$$

2. Alcohols react with phosphorus trichloride or phosphorus pentachloride, forming alkyl halides. Esters of phosphorous and phosphoric acids are intermediate products:

$$C_2H_5OH + PCl_5 \longrightarrow C_2H_5Cl + POCl_3 + HCl.$$

This reaction confirms the conclusion that an alcohol molecule contains a hydroxyl group. A univalent chlorine atom replaces an atom of oxygen and one of hydrogen — a change easily explained under the assumption that the oxygen and hydrogen were present in the form of a univalent group.

3. Acid chlorides and alcohols yield esters:

$$C_2H_5OH + CH_3 \cdot COCl \longrightarrow HCl + C_2H_5 \cdot O \cdot CO \cdot CH_3.$$

This reaction is discussed under esters.

4. Alcohols are susceptible to oxidation. Chromic acid converts ethyl alcohol into acetaldehyde and by the same reagent it is further oxidized to acetic acid. On account of its volatility free acetaldehyde is obtained unless precautions are taken to prevent its escape from the reaction mixture:

$$\underset{\text{Ethyl alcohol}}{CH_3CH_2OH} \longrightarrow \underset{\text{Acetaldehyde}}{CH_3CHO} \longrightarrow \underset{\text{Acetic acid}}{CH_3COOH.}$$

Primary, secondary, and tertiary alcohols may be differentiated by identifying the types of compounds formed from them by oxidation. A primary alcohol is converted into an aldehyde having the same number of carbon atoms as in the alcohol molecule. The aldehyde, in turn, is oxidized to an acid without loss of carbon. A secondary alcohol is oxidized to a ketone having the same number of carbon atoms, but on further oxidation the ketone yields carbon dioxide and water, or acids containing fewer carbon atoms than the ketone itself possessed. A tertiary alcohol is decomposed at once by oxidation to compounds of lower molecular weight.

5. Alcohols are dehydrated by the action of concentrated sulphuric acid, hydrocarbons of the ethylene series being formed:

$$CH_3 \cdot CH_2OH \longrightarrow CH_2 : CH_2 + H_2O.$$

The reaction proceeds even more readily with secondary and tertiary alcohols. By modifying the conditions (controlling the temperature and the concentration of the acid) one molecule of water may be removed from two molecules of alcohol with the production of an ether:

$$2C_2H_5OH \longrightarrow C_2H_5 \cdot O \cdot C_2H_5 + H_2O.$$

An intermediate product, in this case ethyl sulphuric acid, is formed between the alcohol and acid; but it is decomposed by the excess of alcohol, regenerating the acid and forming the ether. The mechanism of the reaction is indicated in the following equations:

$$\text{I.}\quad C_2H_5OH + H_2SO_4 \longrightarrow C_2H_5HSO_4 + H_2O;$$
$$\text{II.}\quad C_2H_5HSO_4 + C_2H_5OH \longrightarrow C_2H_5 \cdot O \cdot C_2H_5 + H_2SO_4.$$

Mixed ethers may be secured by mixing sulphuric acid with the calculated quantity of one alcohol to produce an ester according to I and gradually adding another alcohol during

the process of distillation. Reaction II then occurs with the second alcohol:

$$\underset{\text{Ethyl sulphuric acid}}{C_2H_5HSO_4} + \underset{\text{Propyl alcohol}}{C_3H_7OH} \longrightarrow \underset{\text{Ethylpropyl ether}}{C_2H_5 \cdot O \cdot C_3H_7} + H_2SO_4.$$

Nomenclature. The monohydric alcohols may be named as derivatives of the first member of the series, methyl alcohol, which is called carbinol. Ethyl alcohol is methyl carbinol. An alcohol having the structure $CH_3 \cdot CHOH \cdot CH_2 \cdot CH_3$ is called methyl-ethyl carbinol. According to the Geneva system, the alcohols are named from the corresponding hydrocarbons. The names are made to terminate in *ol.* The same rule applies to polyhydric alcohols, that is, alcohols having more than one hydroxyl in the molecule, the number of such groups being indicated by an appropriate prefix to the terminal *ol.* Thus, CH_3OH is methanol; C_2H_5OH is ethanol; $CH_2OH \cdot CH_2OH$ is ethandiol-1, 2; and $CH_2OH \cdot CH_2 \cdot CHOH \cdot CH_2OH$ is butantriol-1, 3, 4. As in the case of the hydrocarbons the name is derived from the number of carbon atoms in the longest straight chain, and the position of a radical substituted for hydrogen is indicated by a numeral preceding the name of the radical. Numerals following the name indicate positions of groups designated by the name ending. A compound having the structure

$$\begin{array}{c} CH_3-CHOH-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CHOH-CH_2OH \end{array}$$

would be called 3-methyl-pentantriol-2, 4, 5.

METHYL ALCOHOL

Methyl alcohol, CH_3OH, is obtained on a commercial scale from wood by dry distillation. It is commonly called wood alcohol. Among the products found in the distillate are water, acetic acid, methyl alcohol, acetone, and tar. The tar settles out on standing and the liquid layer is siphoned off, treated with lime and water, then redistilled. The lime converts the acetic acid into a non-volatile salt, calcium acetate, and the water throws out of solution hydrocarbons and some other compounds which can be separated by mechanical means from the aqueous solution of methyl alcohol and acetone. By

fractional distillation most of the water is eliminated. Quicklime (CaO) is employed to complete the dehydration of the distillate. The methyl alcohol and acetone may be separated by absorbing the alcohol in calcium chloride. Acetone is pressed out from the solid mass of $CaCl_2 \cdot 4CH_3OH$, and the alcohol is liberated from the calcium chloride by heating with steam. Finally, the alcohol is freed from water by treatment with lime and by distillation.

Methyl alcohol is a colorless liquid (sp. gr. 0. 796 at 20°). It burns with a non-luminous flame, forming carbon dioxide and water. It has a burning taste and is poisonous. A process for making methyl alcohol from carbon monoxide and hydrogen has been developed. The gases are heated to 400° under 150 to 500 atmospheres of pressure in the presence of a catalyst. For details see Lormand, *J. Ind. and Eng. Chem.*, 17, 430 (1925).

ETHYL ALCOHOL

By fermentation glucose is converted into alcohol and carbon dioxide:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \longrightarrow \underset{\text{Alcohol}}{2C_2H_5OH} + 2CO_2.$$

Fermentation is induced by an enzyme, zymase, found in yeast. The fact that yeast acts upon a sugar solution to produce alcohol was observed at a very early date. Fermentation of fruit juices for the production of wine is mentioned in the Bible and in other ancient writings. Tour (1836) was the first to announce the fact that yeast consists of living, growing cells. Leeuwenhoek (1683) gave the first description of its microscopic appearance. Pasteur, in a later period, connected fermentation with the life processes of the yeast plant. He considered the conversion of sugar into alcohol and carbon dioxide to be dependent upon the life and growth of the yeast in the sugar solution. This theory prevailed until Buchner (1897) showed that an extract from yeast containing no living cells could cause fermentation. (See Enzymes, p. 177.)

Starch is the commercial source of the glucose used in the manufacture of alcohol. Potatoes, corn, wheat, or rice may be used as sources of starch. Enzymes contained in sprouting barley, known as diastase and maltase, have the property of catalyzing the hydrolysis of starch, converting it into fermentable sugars, maltose and glucose.

Ground corn is mixed with water and heated an hour or more with steam under about three atmospheres of pressure. After cooling, malt is added and the mixture is held at 63° C. until the starch has been completely hydrolyzed. The iodine test for starch is made from time to time until a sample of the mixture no longer gives the characteristic blue color of starch iodide. The husks of the grain are removed by forcing the mash through a coarse filter. The portion passing through the sieve or filter is conveyed to the fermentation vats. Yeast is added and the temperature is held between 20° and 25° C. until the conversion of sugar to alcohol is complete. This part of the process requires from three to five days. The mash then consists of a slimy fluid mixture of water, alcohol, fusel oil, traces of organic acids and aldehydes, and the solid residue of the grain. From this mixture the alcohol is obtained by distillation. It is not possible to secure absolute alcohol from an aqueous solution of alcohol by distillation alone. A mixture containing 95.5 per cent alcohol and 4.5 per cent water has a maximum vapor pressure and this mixture distills without change in composition at 78.17° C.* In the preparation of absolute alcohol the ordinary 95 per cent product is dehydrated by boiling it, under a reflux condenser, with calcium oxide (quicklime). The water is retained by the lime and the alcohol is liberated from the semi-solid mass by distillation.

Some physical properties of the more important monohydric alcohols are given in the table on the opposite page.

Structural isomerism. There are more isomeric alcohols corresponding to a given empirical formula than there are hydrocarbons having the same number of carbon atoms; for isomerism may be due not only to a branching of the carbon chain but also to a change in the position of the hydroxyl group, or to both of these causes. There are, for example, two butanes:

$$CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_3 \quad \text{and} \quad \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH \cdot CH_3$$

Normal butane — Isobutane

and four butyl alcohols:

I. $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2OH$
Normal primary butyl alcohol

II. $(CH_3)_2CH \cdot CH_2OH$
Isobutyl alcohol

III. $CH_3 \cdot CH_2 \cdot CHOH \cdot CH_3$
Normal secondary butyl alcohol

IV. $(CH_3)_3COH$
Tertiary butyl alcohol

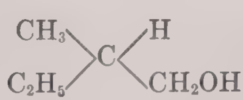
* Noyes and Warfel, *J. Am. Chem. Soc.*, **23**, 463 (1901).

SATURATED MONOHYDRIC ALCOHOLS

NAME	FORMULA	M.P.	B. P.	SP. GR. AT 20°
Methyl alcohol	CH_3OH	–94°	64.5°	0.791
Ethyl alcohol	$CH_3—CH_2OH$	–112°	78.4°	0.789
Propyl alcohols				
n-propyl	$CH_3—CH_2—CH_2OH$	glass	97°	0.804
isopropyl	$CH_3—CHOH—CH_3$	–85.8°	81°	0.789
Butyl alcohols				
n-primary	$CH_3—CH_2—CH_2—CH_2OH$	–79.6°	117°	0.810
n-secondary	$CH_3—CHOH—CH_2—CH_3$	glass	100°	0.808
isobutyl	$(CH_3)_2—CH—CH_2OH$	glass	107°	0.806
trimethylcarbinol	$(CH_3)_3COH$	25.5°	83°	0.786
Amyl alcohols				
n-primary	$CH_3—CH_2—CH_2—CH_2—CH_2OH$		138°	0.815
isobutylcarbinol	$(CH_3)_2—CH—CH_2—CH_2OH$	–134°	131°	0.810
secondarybutylcarbinol	$CH_3—CH(C_2H_5)CH_2OH$		128°	0.816
methylpropylcarbinol	$CH_3—CH_2—CH_2—CHOH—CH_3$		119°	0.817
diethylcarbinol	$C_2H_5—CHOH—C_2H_5$		117°	0.822
methylisopropylcarbinol	$(CH_3)_2CH—CHOH—CH_3$		112°	0.819
dimethylethylcarbinol	$(CH_3)_2—COH—C_2H_5$	–12°	102°	0.812
tertiarybutylcarbinol	$(CH_3)_3C—CH_2OH$	52°	113°	
Higher alcohols				
n-hexyl	$C_6H_{13}OH$		157°	0.820
n-heptyl	$C_7H_{15}OH$	–36.5°	176°	0.821
n-octyl	$C_8H_{17}OH$	–17.9°	195°	0.827
n-nonyl	$C_9H_{19}OH$	–5°	213°	0.828
n-decyl	$C_{10}H_{21}OH$	7°	231°	0.830

Stereoisomerism. According to the structure theory, as developed in the preceding pages, there should be eight and only eight alcohols corresponding to the empirical formula $C_5H_{11}OH$. The eight possible structures are given in the table.

There are, however, three amyl alcohols having the structural formula



The isomerism in this case must be traced to some other cause than differences in the groups attached to the several carbon atoms, for these are identical. It cannot be traced to the influence of multiple bonds, for the compounds are saturated.

Many other cases of this kind are known. There are, for example, three lactic acids having the structure $CH_3 \cdot CHOH \cdot COOH$ and four crystalline tartaric acids having the structure $COOH \cdot CHOH \cdot CHOH \cdot COOH$.

Isomers having the same molecular structure (stereoisomers) have the same melting points and the same solubilities and densities. They differ in no other physical property than that of their action upon plane polarized light. And in this connection there are always pairs of isomers that produce exactly the same angle of rotation, but one member of each pair turns the plane of polarization to the right (dextro-rotation) and the other to the left (lævo-rotation). With the exception of reactions induced by living organisms or by enzymes, they do not differ at all in chemical properties. There are two optically active lactic acids and one inactive acid. The inactive acid, however, is merely a mixture of the two active forms. Such a mixture is said to be *racemic*. By methods to be presented later, the optically active components of the racemic mixture can be separated. Sometimes the *dextro* and the *lævo* forms unite chemically, giving rise to a racemic compound instead of a racemic mixture. In the case of the tartaric acids, we have one dextro and one lævo rotatory compound, a racemic acid (composed of equal quantities of the two active forms) and one acid that is inactive because the two asymmetric groups within the molecule counteract the optical properties of each other. The phenomenon is more fully explained in connection with the isomerism of the dibasic acids and of the carbohydrates.

The fact that light is polarized when it passes through a layer of crystalline tourmaline may be explained by assuming that the portion of the light which actually passes through the layer is due to vibrations of the ether in one plane only. The light before entering the tourmaline is the result of vibrations in all planes that are perpendicular to the path of propagation of the light wave. The emergent ray consists of vibrations in a single plane, all other vibrations having been screened out. This polarized ray will pass through another similar plate of tourmaline, provided the two plates are held in corresponding positions; but if the second plate be slowly turned while the faces of the two are kept parallel to each other, the light emerging from the second plate gradually diminishes in intensity until total darkness is produced with the second tourmaline layer turned through an angle of 90° from the position which it occupied when the light passing through both plates gave the maximum illumination.

In 1815 Biot observed that if a transparent layer of quartz crystal be placed between two tourmaline plates, then the maximum illumination is obtained, not when the tourmaline plates are in corresponding positions, but after one of them has been turned through an angle, the magnitude of which depends upon the thickness of the quartz. In other words, quartz rotates the plane of polarization. Some of his quartz crystals were dextro-rotatory and others were lævo-rotatory. Biot discovered also that solutions of many organic compounds have the same effect. By passing plane polarized light through tubes containing solutions of sugars, salts, and organic acids, he found that some of them were optically active, that is, they turned the plane of polarization either to the right or to the left, but most of them were optically inactive. He discovered that the rotation produced by a solution of an optically active compound is proportional to its concentration and proportional also to the length of the column of solution which the light traverses. He found that the exact angle of rotation is dependent also upon the wave length of the light used.

In 1848 Pasteur, familiar with Biot's work, and knowing that quartz crystallizes in hemihedral forms, reached the conclusion that optical activity might have a definite relationship to crystal form. He observed that the optically active tartaric acids form hemihedral crystals, and he then crystallized a salt of racemic tartaric acid, which has no effect upon plane polarized light, believing that its failure to rotate the plane of polarization would be accompanied by the formation of symmetrical crystals. He was disappointed in finding the same type of crystalline structure as displayed by the optically active tartaric acids. But his careful observation of the crystals revealed the fact that they were not all exactly alike. Some of them differed from others as the right hand differs from the left. The angles between the faces were identical in all of them, but the crystals were not symmetrical and some of them were mirror images of others. He could pick out right-hand and left-hand crystals, and with the aid of a low-power magnifying glass and a pair of tweezers he did this until he had a supply of both kinds. He dissolved the two types of crystals separately and examined the solutions with the aid of a polariscope. One solution was dextro-rotatory. The other was lævo-rotatory. A mixture of equal quantities of the two

solutions was optically inactive. Using the abbreviations *d* and *l* for dextro and lævo, respectively, the inactive acid, consisting of equal quantities of the active forms, is designated *dl*-tartaric acid. The term *racemic* is generally applied to a mixture which is optically inactive because of the presence of exactly equivalent amounts of dextro- and lævo-rotatory forms.

The hemihedral crystals of quartz, some of which were known to be dextro-rotatory and others lævo-rotatory, were likewise found to be enantiomorphous forms, that is, mirror images of each other. In 1873 Wislicenus * published the results of his study of the lactic acids which differ only in their effects upon polarized light, and he made the suggestion that " If it is once granted that molecules can be structurally identical and yet possess dissimilar properties, it can only be explained on the ground that the difference is due to a different arrangement of their atoms in space."

With the work of Pasteur and Wislicenus as a background, van't Hoff and Le Bel independently and simultaneously extended the structure theory to cover cases of optical isomerism. They pointed out the fact that the compounds then known to exhibit optical activity each had at least one carbon atom attached to four different atoms or groups. Thus, for example, in the amyl alcohol called secondary butylcarbinol †

$$\begin{array}{c}CH_3\\C_2H_5\end{array}\!\!>\!C\!<\!\!\begin{array}{c}H\\CH_2OH\end{array}$$

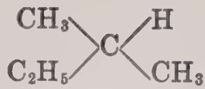
the central carbon atom is attached to four different radicals, namely, CH_3, C_2H_5, H, and CH_2OH. It is said to be an asymmetric carbon atom, and a molecule containing an asymmetric carbon atom usually is optically active. With phosphorus and iodine the alcohol is converted into an iodide

$$\begin{array}{c}CH_3\\C_2H_5\end{array}\!\!>\!C\!<\!\!\begin{array}{c}H\\CH_2I\end{array}$$

* Wislicenus, *Ann.*, **167**, 343 (1873).

† The name "secondary butyl" refers to the radical, $(CH_3)(C_2H_5)CH—$, which is substituted for one hydrogen atom in carbinol, CH_3OH. The amyl alcohol is a primary alcohol. See also the primary alcohol called tertiary butylcarbinol, Table, p. 49.

which is optically active. This in turn may be reduced to the hydrocarbon



There is no asymmetric atom in this hydrocarbon and the compound is inactive.

If we resort to the use of models, and build the three-dimensional structure corresponding to active amyl alcohol or any other molecule containing an atom attached directly to four different groups, we find it possible to make two structures that cannot be superposed upon each other and made to coincide throughout, but which resemble each other as an object resembles its own mirror image. We have then the same difference in structural formula that, in a few instances, is exhibited in crystal form; but our structural formulas apply to liquids and gases, as well as to solids, and they account for optical activity in all phases without reference to crystalline form. One asymmetric carbon atom gives rise to two optically active forms, and one inactive (racemic) mixture of the two. More stereoisomers are possible if the compound has two or more asymmetric atoms.

POLYHYDRIC ALCOHOLS

Polyhydric alcohols are characterized by the presence, in each molecule, of two or more hydroxyl groups. With few exceptions these groups are so distributed that not more than one is held by any single carbon atom. Many reactions are known which might be expected to place two or three hydroxyl groups on the same carbon atom; but almost invariably these reactions lead to the formation of acids, aldehydes, or ketones and water, the hydroxyl groups being completely eliminated or one only being left attached to the carbon.

The dihydric alcohols are known as glycols. Most of the glycols are sweet, colorless liquids. They are soluble in water and boil at higher temperatures than the corresponding monohydric alcohols. They form two series of esters with acids; yield mono- and di-sodium derivatives, and on oxidation they give rise to a variety of products corresponding to different stages in the oxidation process. It is not always practical to

isolate all of the intermediate products. Ethylene glycol, for example, is converted to oxalic acid through the following steps:

$$\underset{\text{Glycol}}{\begin{array}{c}CH_2OH\\ |\\ CH_2OH\end{array}} \longrightarrow \underset{\text{Glycol aldehyde}}{\begin{array}{c}CH_2OH\\ |\\ CHO\end{array}} \longrightarrow \underset{\text{Glyoxal}}{\begin{array}{c}CHO\\ |\\ CHO\end{array}} \longrightarrow \underset{\text{Glyoxalic acid}}{\begin{array}{c}CHO\\ |\\ COOH\end{array}} \longrightarrow \underset{\text{Oxalic acid}}{\begin{array}{c}COOH\\ |\\ COOH\end{array}}.$$

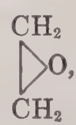
Glyoxal and glyoxalic acid, however, are never made by direct oxidation of the alcohol.

Phosphorus pentachloride or the trichloride will substitute chlorine for both hydroxyl groups in glycol, but hydrogen chloride gas acts upon one of them only:

$$\begin{array}{c}CH_2OH\\ |\\ CH_2OH\end{array} + 2PCl_5 \longrightarrow \underset{\text{Ethylene chloride}}{\begin{array}{c}CH_2Cl\\ |\\ CH_2Cl\end{array}} + 2POCl_3 + 2HCl;$$

$$\begin{array}{c}CH_2OH\\ |\\ CH_2OH\end{array} + HCl \longrightarrow \underset{\text{Ethylene chlorhydrin}}{\begin{array}{c}CH_2Cl\\ |\\ CH_2OH\end{array}} + H_2O.$$

Hydrogen chloride is split off from ethylene chlorhydrin by sodium or potassium hydroxide and ethylene oxide,



is formed. Ethylene oxide (b.p. 14°) reacts rapidly with hydrochloric acid, regenerating ethylene chlorhydrin, or with water to form glycol, or with nascent hydrogen to form ethyl alcohol.

Glycerol or glycerine, $CH_2OH \cdot CHOH \cdot CH_2OH$, a trihydric alcohol, is obtained from fats and oils. (See Esters.) Fats are hydrolyzed by boiling with acids or alkalies, by the action of enzymes, or by treatment with superheated steam. In the latter process the fat is placed in an autoclave and subjected to the action of steam at 315° C. for several hours. The glycerol liberated is purified by distillation in partial vacuum. It is a heavy, oily, viscous liquid. It is miscible with water in all proportions and has a sweet taste. It melts at 17° C. and boils at 290° C. It is formed when sugar undergoes alcoholic

fermentation, the quantity produced varying from one to three per cent of the weight of the sugar.

Glycerol is used in the manufacture of inks, confectionery, and many pharmaceutical preparations. Its most valuable compounds are the natural and artificial esters in which glycerol is combined with acids. The important esters of glycerol occurring in nature are the animal and vegetable fats and oils. The chief artificial preparation is nitroglycerine.

A mixture of glycerol and solid potassium permanganate takes fire spontaneously. In aqueous solution the rate of the reaction can be controlled and tartronic acid is produced. Oxidation with mercuric oxide yields glyceric acid only.

$$\begin{array}{lclcl}
CH_2OH & & COOH & & COOH \\
| & & | & & | \\
CHOH & \longrightarrow & CHOH & \longrightarrow & CHOH \\
| & & | & & | \\
CH_2OH & & CH_2OH & & COOH \\
\text{Glycerol} & & \text{Glyceric acid} & & \text{Tartronic acid}
\end{array}$$

Glyceric acid is a sirupy liquid which does not crystallize. Tartronic acid crystallizes in large colorless prisms that melt at 184°. Both are soluble in water and alcohol and both decompose below 200°.

Erythritol, $CH_2OH \cdot CHOH \cdot CHOH \cdot CH_2OH$, a tetrahydric alcohol, occurs in many seaweeds. It is a sweet crystalline solid (m.p. 126°, b.p. 330°).

Arabitol and xylitol are isomeric pentahydric alcohols. Arabitol is a crystalline substance melting at 102°. Xylitol is a sirupy liquid. Both are soluble in water and their solutions are sweet. They are obtained by reducing the sugars, arabinose and xylose. They are both represented by the formula:

$$CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CH_2OH.$$

Mannitol, dulcitol, and sorbitol are isomeric hexatomic alcohols:

$$CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CH_2OH.$$

They are obtained by reducing hexoses of corresponding structures. Mannitol occurs in manna, the sap of certain species of ash. It is extracted from manna with hot alcohol, from which it crystallizes on cooling.

The most important polyhydric alcohols are those that have the carbonyl group (—CO—) in addition to hydroxyl groups. They are aldehydes or ketones as well as alcohols. The sugars belong to this group. They are considered in the chapter on Carbohydrates.

UNSATURATED ALCOHOLS

The unsaturated alcohol corresponding to the simplest possible structure, $CH_2{=}CHOH$, has not been prepared. All attempts to produce it have resulted in the formation of acetaldehyde, $CH_3{-}CHO$. The hydroxyl group is rarely held by carbon which is attached by two bonds to another carbon atom. Such compounds are, no doubt, produced in numerous reactions, but an immediate intramolecular rearrangement gives rise to the more stable form.

Allyl alcohol, $CH_2{=}CH{-}CH_2OH$, a colorless liquid (b.p. 96.6°, sp. gr. 0.872), is prepared by heating glycerol with oxalic acid. Oxalic acid is decomposed by heat into formic acid and carbon dioxide. Formic acid and glycerol form an ester called monoformin, but at temperatures higher than 215° the ester decomposes into carbon dioxide, water, and allyl alcohol. At a lower temperature monoformin is readily hydrolyzed to formic acid and glycerol:

$$\underset{\text{Glycerol}}{\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array}} \xrightarrow{H\cdot COOH} \underset{\text{Monoformin}}{\begin{array}{l} CH_2OCHO \\ | \\ CHOH \\ | \\ CH_2OH \end{array}} \xrightarrow{\text{heat}} \underset{\text{Allyl alcohol}}{\begin{array}{l} CH_2 \\ \| \\ CH \\ | \\ CH_2OH \end{array}} + CO_2 + H_2O.$$

According to the structure theory three different allyl alcohols might exist, namely, $CH_2{=}CH{-}CH_2OH$, $CH_2{=}COH{-}CH_3$, and $CHOH{=}CH{-}CH_3$. Only the first is known. The second and third formulas would require the attachment of hydroxyl to unsaturated carbon. If the second compound were formed, it would rearrange to $CH_3{-}CO{-}CH_3$, a stable substance known as acetone; and the third would change to propionaldehyde, $CHO{-}CH_2{-}CH_3$.

Propargyl alcohol, $HC{\equiv}C{-}CH_2OH$, is a colorless liquid boiling at 115°. It forms explosive metallic derivatives corresponding to the silver and copper salts of acetylene. With chlorine and bromine the unsaturated alcohols form addition products.

ETHERS

The aliphatic ethers are alkyl oxides corresponding to the general formula $R \cdot O \cdot R'$. The two alkyl radicals may be alike or different. The ethers of low molecular weight are derived from alcohols through the elimination of one molecule of water from two molecules of alcohol. Thus, from methyl alcohol we obtain dimethyl ether and from ethyl alcohol diethyl ether.

$$2CH_3OH \longrightarrow CH_3 \cdot O \cdot CH_3 + H_2O$$
$$2C_2H_5OH \longrightarrow C_2H_5 \cdot O \cdot C_2H_5 + H_2O$$

Preparation. 1. The formation of an ether from an alcohol by treatment with sulphuric acid is accomplished in two stages. In the first step sulphuric acid combines with the alcohol, forming an alkylsulphuric acid, and in the second step this intermediate product reacts with more alcohol, forming an ether and regenerating sulphuric acid. Thus, in the preparation of ordinary ether from ethyl alcohol, we have

$$C_2H_5OH + H_2SO_4 \longrightarrow \underset{\text{Ethylsulphuric acid}}{C_2H_5HSO_4} + H_2O, \qquad (1)$$

$$C_2H_5HSO_4 + C_2H_5OH \longrightarrow \underset{\text{Diethyl ether}}{C_2H_5 \cdot O \cdot C_2H_5} + H_2SO_4. \qquad (2)$$

In the practical procedure the alcohol and acid are mixed in molecular proportions and heated in a distilling flask to 140°. More alcohol is then allowed to flow into the mixture as rapidly as ether distills out.

Only ethers of low molecular weight can be made in this manner, for the alcohols having more than three carbon atoms all react with sulphuric acid to form unsaturated hydrocarbons. At higher temperatures the alcohols of low molecular weight also yield unsaturated hydrocarbons. At 170° ethylsulphuric acid is decomposed with the production of ethylene, hence it is important to control the temperature in the manufacture of ether.

The sulphuric acid used in equation (1) is regenerated in the second step (2) and the process can be carried on without interruption until approximately fifteen times as much alcohol as represented in equation (1) has been used. The reaction finally stops on account of dilution with the water formed. Sulphur dioxide and other by-products are formed in small amounts, due to oxidation of some of the alcohol by the hot sulphuric acid. Ethyl sulphuric acid reacts with water as follows:

$$C_2H_5HSO_4 + HOH \longrightarrow C_2H_5OH + H_2SO_4. \qquad (3)$$

This is a reversal of equation (1). The velocity of this reaction (3) increases as the concentration of water in the mixture increases. It gradually approaches the velocity of the reverse process (1) and finally a practical limit is reached, beyond which it is not economical to force the reaction by further additions of alcohol.

A mixed ether, that is, one containing two different alkyl radicals, can be made by forming the alkylsulphuric acid with one alcohol and mixing the product with another alcohol before distilling.

$$C_2H_5OH + H_2SO_4 \longrightarrow C_2H_5HSO_4 + H_2O$$
$$CH_3OH + C_2H_5HSO_4 \longrightarrow \underset{\text{Methylethyl ether}}{CH_3 \cdot O \cdot C_2H_5} + H_2SO_4$$

The process, however, yields more than one ether. In this case dimethyl ether and diethyl ether are contaminating by-products of the reaction.

2. An ether is formed when a mixture of an alkyl halide and an alcoholate is distilled.

$$C_2H_5I + C_3H_7ONa \longrightarrow C_2H_5 \cdot O \cdot C_3H_7 + NaI$$

This is the most satisfactory method for making ethers of high molecular weight.

3. Ethers have been made by heating alkyl halides with silver oxide.

$$2C_2H_5I + Ag_2O \longrightarrow C_2H_5 \cdot O \cdot C_2H_5 + 2AgI$$

This method has no practical value.

4. Phosphoric acid may be substituted for sulphuric acid in the preparation of an ether from an alcohol of low molecular weight.

ETHERS

Name	Formula	B.P.	Sp. Gr.
Dimethyl ether . . .	$CH_3 \cdot O \cdot CH_3$	– 23.6°	
Methyl-ethyl ether . .	$CH_3 \cdot O \cdot C_2H_5$	10.8°	0.725 (0°)
Diethyl ether	$C_2H_5 \cdot O \cdot C_2H_5$	34.6°	0.718 (15.6°)
Methyl-*n*-propyl ether .	$CH_3 \cdot O \cdot C_3H_7$	38.9°	0.747 (0°)
Methyl-isopropyl ether .	$CH_3 \cdot O \cdot C_3H_7$	32.5°	0.735 (20°)
Ethyl-*n*-propyl ether . .	$C_2H_5 \cdot O \cdot C_3H_7$	64°	0.739 (20°)
Ethyl-isopropyl ether .	$C_2H_5 \cdot O \cdot C_3H_7$	54°	0.745 (0°)
Dipropyl ether . . .	$C_3H_7 \cdot O \cdot C_3H_7$	90.7°	0.763 (0°)
Diisopropyl ether . . .	$C_3H_7 \cdot O \cdot C_3H_7$	69°	0.743 (0°)
Ethyl-*n*-butyl ether . .	$C_2H_5 \cdot O \cdot C_4H_9$	92°	0.769 (0°)
Ethyl-isobutyl ether . .	$C_2H_5 \cdot O \cdot C_4H_9$	80°	0.751
Ethyl-tertiarybutyl ether	$C_2H_5 \cdot O \cdot C_4H_9$	141°	0.784 (0°)
Di-*n*-butyl ether . . .	$C_4H_9 \cdot O \cdot C_4H_9$	121°	0.756 (21°)
Diisobutyl ether . . .	$C_4H_9 \cdot O \cdot C_4H_9$	122°	0.762 (15°)
Diisoamyl ether . . .	$C_5H_{11} \cdot O \cdot C_5H_{11}$	173°	0.781 (15°)

Properties. Dimethyl ether is a gas. All other ethers included in the table are colorless liquids. Some higher members of the series are crystalline solids. The ethers are all lighter than water and very slightly soluble in water. They are soluble in alcohols, hydrocarbons, chloroform, and other organic liquids. There are very few general reactions of the ethers, for they are inert compounds. They are not attacked by alkalies nor by the free alkali metals. They are unaffected by cold phosphorus pentachloride, dilute acids, and mild oxidizing and reducing agents.

Hot concentrated nitric acid or chromic acid converts an ether into the same oxidation products that would be obtained from the corresponding alcohol. Prolonged heating with concentrated sulphuric acid converts diethyl ether into ethyl sulphuric acid with the ultimate production of ethylene.

$$(C_2H_5)_2O + 2H_2SO_4 \longrightarrow 2C_2H_5HSO_4 + H_2O.$$
$$C_2H_5HSO_4 \longrightarrow C_2H_4 + H_2SO_4.$$

The decomposition of an ether is much more readily accomplished through the action of hot hydrogen iodide.

$$R \cdot O \cdot R + HI \longrightarrow ROH + RI.$$
$$R \cdot O \cdot H + HI \longrightarrow HOH + RI.$$

Ethyl ether. Diethyl ether is the most important representative of the group. It is manufactured from alcohol and sul-

phuric acid in large quantities for use as an anæsthetic and as a solvent for organic preparations. It is freed from sulphur dioxide by washing with an aqueous alkaline solution. The commercial product usually contains small quantities of alcohol and water. When pure ether is required, the washed ether is shaken with granular calcium chloride to remove most of the water and alcohol and then allowed to stand in contact with sodium wire as long as hydrogen is evolved. It is then distilled under anhydrous conditions.

Ethyl ether is a light, colorless, mobile liquid. It dissolves in 11.1 times its own volume of water at 25°. Ether at the same temperature dissolves two per cent of its own volume of water. On account of its high vapor pressure at ordinary temperatures, and the fact that its vapor forms an explosive mixture with air, ether must be kept away from flames.

ALKYL HALIDES

The alkyl radicals in combination with fluorine, chlorine, bromine, and iodine form compounds known collectively as the alkyl halides. The direct substitution of fluorine, chlorine, or bromine for hydrogen in a hydrocarbon is easily accomplished. Iodine derivatives are prepared by indirect methods only. The action of phosphorus and iodine or of phosphorus triiodide on an alcohol constitutes a satisfactory laboratory method for making alkyl iodides: *

$$PI_3 + 3C_2H_5OH \longrightarrow 3C_2H_5I + H_3PO_3.$$

Chlorides and bromides may be made in the same way by using PCl_3 and PBr_3, respectively. Hydrogen halide is liberated at the same time and, therefore, the above equation does not indicate all that happens.

At moderately low temperatures an ester of phosphorous acid may be isolated and it is probably the first reaction product formed under any circumstances.

$$PCl_3 + 3C_2H_5OH \longrightarrow P(OC_2H_5)_3 + 3HCl.$$

When heated with a halogen acid the ester yields free phosphorous acid and an alkyl halide.

Dehn and Davis† have obtained superior yields of alkyl chlorides by the use of zinc chloride in conjunction with the alcohol and phosphorus trichloride.

Alkyl halides are formed from unsaturated hydrocarbons by the direct addition of hydrogen halide. (See p. 35.)

$$CH_2 : CH_2 + HBr \longrightarrow CH_3 \cdot CH_2Br.$$

Alkyl halides are formed by the action of halogen acids on alcohols. Using the symbol R for any alkyl radical, and X for either of the halogens, we may write the general equation:

$$\underset{\text{Alcohol}}{ROH} + \underset{\text{Acid}}{HX} \rightleftarrows \underset{\text{Alkyl halide}}{RX} + \underset{\text{water}}{HOH}.$$

* Adams and Vorhees, *J. Am. Chem. Soc.*, **41**, 789 (1919).
† Dehn and Davis, *J. Am. Chem. Soc.*, **29**, 1328 (1908).

A reversible reaction, of this kind, reaches equilibrium when the rate of transformation in one direction is exactly equal to the rate of change in the reverse order. Representing the molal concentration of the alcohol by a, that of the acid by b, and the mols per liter of alkyl halide and water by c and d, respectively, equilibrium is established when $\frac{cd}{ab} = k$. For every reversible reaction there is a definite numerical value of k, the equilibrium constant, which can be determined experimentally. With k known, the equation affords a means of estimating the quantity of each product that will be formed from any given mixture.

At the beginning of the reaction, indicated above, c and d are equal to zero and the reaction proceeds from left to right only. As soon as c and d reach finite values the reverse reaction begins and it continues with increasing velocity as the product cd increases. The velocity of the forward reaction is retarded as the product ab diminishes, until the value of k is reached. If x is the number of mols of ROH transformed in time t, it is also the number of mols of HX used, and the velocity constant, k_1, is given by the differential equation:

$$\frac{dx}{dt} = k_1(a - x)(b - x).$$

The rate of change in the reverse order is:

$$\frac{-dx}{dt} = k_2(c + x)(d + x).$$

The apparent rate of change in either direction at any instant is the difference between the rates of the two opposing reactions, and at equilibrium the apparent rate of change is zero. The system has not reached a static condition, however. Both reactions are going on, but with equal velocities. The equilibrium constant, k, is a ratio between the velocity constants of the opposing reactions:

$$k = \frac{k_1}{k_2}.$$

Properties. Methyl chloride, ethyl chloride, and methyl bromide are gases under ordinary conditions of temperature and pressure. All others included in the table are liquids; the higher members are solids. In each group the densities decrease as the molecular weights increase. In other words, the specific gravity is roughly proportional to the per cent of halogen in the molecule. The alkyl halides are almost insoluble in water but they dissolve readily in alcohol, ether, benzene, and other organic solvents. They do not ionize as pure-liquids nor in solution, yet they take part in many types of reactions that involve the removal of the halogen and substitution of other elements or groups. Most of these reactions are slow, incomplete, and reversible. There is a lack of uniformity in the behavior of these compounds. Ethyl iodide,

ALKYL HALIDES

Alkyl Group	Chlorides			Bromides		Iodides	
	Formula	B.P.	Sp. Gr.	B.P.	Sp. Gr.	B.P.	Sp. Gr.
Methyl	CH_3X	−24°	0.952 (0°)	4.5°	1.732 (0°)	45°	2.293 (18°)
Ethyl	CH_3CH_2X	12.5°	0.918 (8°)	38.4°	1.468 (13°)	72.3°	1.944 (14°)
n-Propyl	$CH_3CH_2CH_2X$	46.5°	0.912 (0°)	71°	1.383 (0°)	102.5°	1.786 (0°)
iso-Propyl	CH_3CHXCH_3	36.5°	0.882 (0°)	59°	1.340 (0°)	89°	1.774 (0°)
n-Butyl	$CH_3CH_2CH_2CH_2X$	77.5°	0.907 (0°)	101°	1.305 (0°)	129.6°	1.643 (0°)
iso-Butyl	$(CH_3)_2CHCH_2X$	68.5°	0.895 (0°)	92°	1.204 (16°)	119°	1.640 (0°)
Secondary butyl	$CH_3CH_2CHXCH_3$	—	—	—	—	120°	1.626 (0°)
Tertiary butyl	$(CH_3)_3CX$	55°	0.866 (0°)	72°	1.215 (20°)	100°	1.571 (0°)
Normal amyl	$CH_3(CH_2)_3CH_2X$	107°	0.901 (0°)	129°	1.246 (0°)	156°	1.543 (0°)
iso-Amyl	$(CH_3)_2CHCH_2CH_2X$	101°	0.893 (0°)	121°	1.236 (0°)	148°	1.468 (0°)
Tertiarybutylmethyl	$(CH_3)_3CCH_2X$	—	0.879 (0°)	—	1.225 (0°)	—	—
Active amyl	$(CH_3)(C_2H_5)CHCH_2X$	99°	0.886 (15°)	120°	1.221 (20°)	148°	1.524 (20°)
Normal hexyl	$CH_3(CH_2)_4CH_2X$	134°	0.892 (16°)	156°	1.193 (0°)	182°	1.461 (0°)
Normal heptyl	$CH_3(CH_2)_5CH_2X$	159°	0.881 (16°)	179°	1.113 (16°)	201°	1.386 (16°)
Normal octyl	$CH_3(CH_2)_6CH_2X$	180°	0.880 (16°)	199°	1.116 (16°)	221°	1.345 (16°)

for example, reacts promptly with silver nitrate, yielding a precipitate of silver iodide. Other alkyl iodides either fail to react with silver ions or do so very slowly. Ethyl chloride forms no precipitate even when heated under pressure with silver nitrate.

Ethyl chloride is prepared in large quantities for use as a local anæsthetic. It is placed on the market in small glass tubes each provided with a capillary opening from which the liquid is sprayed upon the tissue to be frozen. The anæsthesia is produced, not by virtue of any chemical property of ethyl chloride, but merely by chilling caused by the rapid absorption of heat from the tissue by the very volatile liquid as it vaporizes.

TYPICAL REACTIONS OF ALKYL HALIDES

The alkyl halides are of great importance as sources of various types of compounds prepared as indicated by the following general reactions. These reactions will be considered in detail later.

Cyanides:

$RX + KCN \longrightarrow RCN + KX$ (p. 141)

Alcohols:

$RX + AgOH \longrightarrow ROH + AgX$ (p. 43)

Magnesium alkyl halides:

$RX + Mg \longrightarrow RMgX$ (p. 82)

Zinc alkyls:

$2RX + 2Zn \longrightarrow ZnR_2 + ZnX_2$ (p. 312)

Mercaptans:

$RX + KSH \longrightarrow RSH + KX$

Ethers:

$RX + RONa \longrightarrow ROR + NaX$ (p. 49)

Thioethers:

$RX + RSNa \longrightarrow RSR + NaX$

Hydrocarbons (*saturated*):

$RX + 2H \longrightarrow RH + HX$ (p. 407)

$2RX + Zn \text{ or } Na \longrightarrow RR + ZnX_2 \text{ or } NaX$ (p. 23)

Hydrocarbons (*unsaturated*):

$R{-}CH_2{-}CH_2X + KOH \text{ in alcohol} \longrightarrow R{-}CH{=}CH_2$ (p. 32)

Amines:

$RX + NH_3 \longrightarrow RNH_2 \cdot HX$ (p. 72)

Esters:

$RX + R' \cdot COOK \longrightarrow R' \cdot COOR + KX.$

PARAFFIN POLYHALIDES

Chloroform, $CHCl_3$ (m.p. $-70°$, b.p. $61°$), is a heavy, colorless liquid possessing an agreeable odor and a sweet taste. It produces a burning sensation in the mouth. It is an excellent solvent for fats and many other types of compounds. It is still used extensively as an anæsthetic. Its effect upon the heart, however, renders its use dangerous. Ether is safer and is rapidly replacing chloroform as a general anæsthetic.

Chloroform is prepared by distilling a mixture of fresh bleaching powder and alcohol, or by warming chloral hydrate with a base. The conversion of alcohol into chloroform is accomplished in at least three steps usually represented by the following equations:

$$2CH_3 \cdot CH_2OH + Ca(OCl)_2 \longrightarrow 2CH_3 \cdot CHO + CaCl_2 + 2H_2O;$$
$$2CH_3 \cdot CHO + 3Ca(OCl)_2 \longrightarrow 2CCl_3 \cdot CHO + 3Ca(OH)_2;$$
$$2CCl_3 \cdot CHO + Ca(OH)_2 \longrightarrow 2CHCl_3 + (HCOO)_2Ca.$$

The evidence in support of this mechanism is inconclusive. The three equations do not tell the whole story, for compounds not included in the equations occur as by-products of the reaction. It is certain, however, that any source of free chlorine serves to convert alcohol into trichloracetaldehyde which, in turn, reacts with any base to form chloroform and a formate.

Alcoholic potash converts chloroform into a formate and chloride of the alkali metal:

$$CHCl_3 + 4KOH \longrightarrow HCOOK + 3KCl + 2H_2O.$$

Chloroform acts on primary amines in the presence of an alcoholic solution of a base, forming carbylamines. These compounds are characterized by disagreeable odors detectable in extremely small quantities. The reaction affords a qualitative test for chloroform or for a primary amine:

$$CHCl_3 + 3KOH + C_6H_5NH_2 \longrightarrow C_6H_5NC + 3KCl + 3H_2O.$$

When exposed to light and air chloroform is slowly oxidized to phosgene and other products:

$$CHCl_3 + \tfrac{1}{2}O_2 \longrightarrow COCl_2 + HCl.$$

Vigorous oxidizing agents, such as chromic acid and perchloric acid, rapidly bring about the same change.

Chloral, CCl_3CHO (b.p. 97°, sp. gr. 1.512 at 20°), is a colorless, oily liquid possessing a penetrating odor. It is formed in a slow reaction between chlorine and alcohol. Some of the alcohol is oxidized to acetaldehyde, which condenses with unchanged alcohol, forming an acetal. The latter reacts with chlorine, yielding trichloracetal. In the presence of hydrochloric acid (which is formed in the chlorinating process) trichloracetal is converted into a crystalline product known as chloral alcoholate. This in turn is hydrolyzed to chloral.

$$CH_3\cdot CH_2OH + Cl_2 \longrightarrow CH_3\cdot CHO + 2HCl; \qquad (1)$$

$$CH_3\cdot CHO + 2C_2H_5OH \longrightarrow CH_3\cdot C\begin{array}{l}\diagup OC_2H_5\\ -H\\ \diagdown OC_2H_5\end{array} + H_2O; \qquad (2)$$

$$CH_3\cdot C\begin{array}{l}\diagup OC_2H_5\\ -H\\ \diagdown OC_2H_5\end{array} + 3Cl_2 \longrightarrow CCl_3\cdot C\begin{array}{l}\diagup OC_2H_5\\ -H\\ \diagdown OC_2H_5\end{array} + 3HCl; \qquad (3)$$

$$CCl_3\cdot C\begin{array}{l}\diagup OC_2H_5\\ -H\\ \diagdown OC_2H_5\end{array} + HCl \longrightarrow CCl_3\cdot C\begin{array}{l}\diagup OH\\ -H\\ \diagdown OC_2H_5\end{array} + C_2H_5Cl; \qquad (4)$$

$$CCl_3\cdot C\begin{array}{l}\diagup OH\\ -H\\ \diagdown OC_2H_5\end{array} + H_2O \longrightarrow \underset{\text{Chloral hydrate}}{CCl_3\cdot C\begin{array}{l}\diagup OH\\ -H\\ \diagdown OH\end{array}} + C_2H_5OH. \qquad (5)$$

The dihydroxy compound, chloral hydrate, loses water when warmed with concentrated sulphuric acid and distills over as free choral. In the absence of dehydrating agents chloral takes up a molecule of water, forming the hydrate, a colorless crystalline solid (m.p. 57°). This process of crystallization, followed by dehydration, affords the best means of purifying chloral.

Chloral hydrate is one of the very few examples of a stable compound with two hydroxyl groups held by the same carbon atom. The compound is used extensively in medicine as a soporific.

Chloral is decomposed rapidly and quantitatively by a hot solution of potassium hydroxide. The reaction constitutes a good method for obtaining pure chloroform:

$$CCl_3CHO + KOH \longrightarrow CHCl_3 + HCOOK.$$

Bromoform, $CHBr_3$ (m.p. 7.8°, b.p. 151° sp. gr. 2.9), is made from acetone or alcohol through the action of bromine and potassium hydroxide.

Iodoform, CHI_3 (m.p. 120°), is prepared from alcohol by treatment with iodine and potassium hydroxide. Acetone or any other ketone having the $CH_3CO—$ group may be substituted for alcohol:

$$CH_3 \cdot CO \cdot CH_3 + 3KOI \longrightarrow CH_3 \cdot COOK + CHI_3 + 2KOH.$$

Iodoform crystallizes in yellow plates. It has a persistent odor, resembling that of saffron. It has antiseptic properties and is used as a germicide. It is soluble in alcohol and ether but insoluble in water.

Iodoform yields crystalline addition products with amines* corresponding to the formulas $RNH_2 \cdot CHI_3$, $(RNH_2)_2CHI_3$, and $(RNH_2)_3CHI_3$. Their formation is catalyzed by light.

Chlorpicrin, or nitrochloroform, CCl_3NO_2, a colorless liquid (b.p. 112°, sp. gr. 1.692 at 0°), is prepared from chloral and nitric acid. Its vapor attacks the mucus membrane of the eye and it has been used as a lachrymator in gas warfare. It explodes when heated. It is reduced by iron and acetic acid to methylamine:

$$CCl_3NO_2 + 6H_2 \longrightarrow CH_3NH_2 + 3HCl + 2H_2O.$$

Carbon tetrachloride, CCl_4, is made from carbon bisulphide by treatment with chlorine:

$$CS_2 + 3Cl_2 \longrightarrow CCl_4 + S_2Cl_2.$$

The sulphur chloride is removed by shaking the mixed products with a solution of sodium hydroxide, or it may be used as a source of chlorine by boiling with an excess of carbon bisulphide. Sulphur is precipitated and an additional yield of carbon tetrachloride is obtained:

$$CS_2 + 2S_2Cl_2 \longrightarrow CCl_4 + 6S.$$

* Dehn and Conner, *J. Am. Chem. Soc.*, **34**, 1409 (1912).

Carbon tetrachloride may be made also by passing chlorine gas into hot chloroform. It is decomposed by hot alcoholic potash:

$$CCl_4 + 6C_2H_5OK + 3H_2O \longrightarrow K_2CO_3 + 4KCl + 6C_2H_5OH.$$

It is used as a solvent and as a fire extinguisher.

Ethylene chloride, $CH_2Cl \cdot CH_2Cl$, is prepared by the action of nascent chlorine on ethylene. Ethylene gas is passed into a warm mixture of manganese dioxide, sodium chloride, and 60 per cent sulphuric acid.

Ethylene bromide, $CH_2Br \cdot CH_2Br$ (m.p. 9°), is usually prepared by passing ethylene into bromine under water. The action is catalyzed by sunlight. The product is a colorless, oily liquid almost insoluble in water.

Ethylene iodide, $CH_2I \cdot CH_2I$ (m.p. 81°), is made by the action of ethylene on a paste of iodine in alcohol.

PARAFFIN POLYHALIDES

	Chlorides	B.P.	Bromides	B.P.
Methylene chloride . .	CH_2Cl_2	42°	CH_2Br_2	98°
Chloroform	$CHCl_3$	61°	$CHBr_3$	151°
Tetrachlormethane . .	CCl_4	76°	CBr_4	189°
Ethylidene chloride .	$CH_3 \cdot CHCl_2$	58°	$CH_3 \cdot CHBr_2$	112°
Ethylene dichloride . .	$CH_2Cl \cdot CH_2Cl$	84°	$CH_2Br \cdot CHBr$	131°
Vinyl trichloride . . .	$CH_2Cl \cdot CHCl_2$	114°	$CH_2Br \cdot CHBr_2$	188°
Methyl chloroform . .	$CH_3 \cdot CCl_3$	74°	$CH_3 \cdot CBr_3$	
Acetylene tetrachloride	$CHCl_2 \cdot CHCl_2$	147°	$CHBr_2 \cdot CHBr_2$	114°*
Pentachlorethane . .	$CHCl_2 \cdot CCl_3$	159°	$CHBr \cdot CBr_3$	103°*
Hexachlorethane . .	$CCl_3 \cdot CCl_3$	187°	$CBr_3 \cdot CBr_3$	decomp.
Propylidene chloride .	$CH_3 \cdot CH_2 \cdot CHCl_2$	86°	$CH_3 \cdot CH_2 \cdot CHBr_2$	130°
1, 2, Dichlorpropane .	$CH_3 \cdot CHCl \cdot CH_2Cl$	97°	$CH_3 \cdot CHBr \cdot CH_2Br$	141°
Trimethylene chloride .	$CH_2Cl \cdot CH_2 \cdot CH_2Cl$	120°	$CH_2Br \cdot CH_2 \cdot CH_2Br$	165°

* At 13 m.m. Hg. pressure.

NITRO-PARAFFINS

A nitro-paraffin is a derivative of an aliphatic hydrocarbon in which hydrogen has been replaced by the NO_2 group, the nitrogen being directly attached to carbon. The nitro-compounds are isomeric with the alkyl nitrites in which nitrogen atoms are linked to carbon through oxygen. When alkyl halides react with silver nitrite usually mixtures of these isomers are formed:

$$C_2H_5I + AgNO_2 \longrightarrow C_2H_5NO_2 + AgI;$$
$$C_2H_5I + AgNO_2 \longrightarrow C_2H_5ONO + AgI.$$

The normal alkyl halides up to and including butyl compounds yield principally nitro-compounds; but those of higher molecular weight give mixtures in which either form may predominate. All secondary halides (halogens attached to secondary carbon atoms) yield similar mixtures, but tertiary halides form nitrites almost exclusively.

The isomers are readily separated by distillation, the nitro-compound boiling at a higher temperature than the corresponding nitrite in every case. Nitromethane, for instance, boils at 101° and methyl nitrite at −12°. The ethyl derivatives boil at 113° and 16°, respectively. Each member of the high-boiling series can be reduced to an amine, indicating direct union between carbon and nitrogen; and each member of the low-boiling group can be hydrolyzed to an alcohol and nitrous acid, indicating that they are, in fact, nitrous esters.

Nitro-paraffins having hydrogen and NO_2 attached to the same carbon dissolve in alkalies, forming metallic derivatives. These salts react with bromine, the metal being replaced by the halogen. But the addition of an acid to the salt does not regenerate the original nitro-body; an aldehyde or ketone and nitrous oxide appear instead. Nef * regarded this as evidence of a double bond between the nitrogen and carbon and

* Nef, *Ber.*, **29**, 1218 (1896)

assumed a tautomerism * in the case of nitro-paraffins as indicated below:

$$CH_3 \cdot CH_2 \cdot N \Big\langle \begin{array}{l} O \\ O \end{array} \rightleftarrows CH_3 \cdot CH : N \Big\langle \begin{array}{l} O \\ OH \end{array}$$

$$\begin{array}{l} CH_3 \\ CH_3 \end{array} \Big\rangle CH \cdot N \Big\langle \begin{array}{l} O \\ O \end{array} \rightleftarrows \begin{array}{l} CH_3 \\ CH_3 \end{array} \Big\rangle C : N \Big\langle \begin{array}{l} O \\ OH \end{array}$$

$$\begin{array}{l} CH_3 \\ CH_3 \\ CH_3 \end{array} \Bigg\rangle C \cdot N \Big\langle \begin{array}{l} O \\ O \end{array} \longrightarrow \text{(No change).}$$

The primary and secondary nitro-compounds thus form pseudo acids. No such possibility exists for the tertiary nitro-body. This explains why the nitro-compounds having hydrogen on the same carbon with the NO_2 dissolve in alkalies, whereas tertiary nitro-compounds are insoluble. The sodium salt of a primary nitro-paraffin has the formula,

$$R \cdot CH : N \Big\langle \begin{array}{l} O \\ ONa \end{array}$$

and when acidified this yields the pseudo acid,

$$R \cdot CH : N \Big\langle \begin{array}{l} O \\ OH \end{array}$$

The pseudo acid is capable of conversion into the original nitro-compound, and this change occurs slowly in neutral solution; but at ordinary temperatures, in the presence of an excess of acid, it decomposes into an aldehyde and hyponitrous acid. The latter breaks up at once into nitrous oxide and water:

$$2R \cdot CH : N \Big\langle \begin{array}{l} O \\ OH \end{array} \longrightarrow 2R \cdot CHO + \begin{array}{c} NOH \\ \| \\ NOH \end{array} \quad (N_2O + H_2O).$$

* Two or more compounds may have the same composition and the same molecular weight but have different properties as a result of differences in molecular structure. If, in such a group, each molecular structure is stable and does not change rapidly from one form to another, we call the compounds isomers. On the other hand, if such compounds have a tendency to undergo changes in structure so that one form is readily converted into another, and especially if the change in structure is rapid and reversible, we call the compounds tautomers. Tautomers are not easily separated. A reagent which acts specifically with one form of the compound will not accomplish the separation, for as fast as the active member is removed, the equilibrium between the tautomeric forms is disturbed and the unreactive members of the group spontaneously change to the active form.

Hantzsch confirmed this theory by isolating both tautomeric forms of phenyl nitromethane. Carbon dioxide was passed into a solution of its sodium salt and a yellow oil gradually separated from the mixture. Hydrochloric acid, on the other hand, decomposed the sodium salt with an immediate precipitation of a colorless crystalline compound. The oil and the crystals had the same composition and molecular weight. The solid gave the ferric chloride and phenyl isocyanate tests for hydroxyl, dissolved rapidly in alkali, and had an acid reaction. The oil possessed none of these properties. It dissolved very slowly in alkaline solutions, indicating a gradual change in structure, and when it was finally all dissolved, hydrochloric acid reprecipitated it in the crystalline form:

$$\underset{\text{Yellow oil}}{C_6H_5 \cdot CH_2 \cdot N\begin{matrix}\nearrow O \\ \searrow O\end{matrix}} \rightleftarrows \underset{\text{Colorless crystals}}{C_6H_5 \cdot CH : N\begin{matrix}\nearrow O \\ \searrow OH\end{matrix}}.$$

The oil is more stable than the solid isomer and on standing a week or more the crystalline form disappears, equilibrium being established with nearly all of the substance in the form of the true nitro-compound. The time required to establish equilibrium may be reduced to an hour or two by warming an alcoholic solution of the crystals.

In their reactions with nitrous acid there is a close analogy between the nitro-paraffins and the aliphatic amines. The primary nitro-compounds yield nitrolic acids, secondary compounds yield nitroso-nitro-paraffins (colorless solids that impart a blue color to chloroform) and the tertiary nitro-bodies do not react with nitrous acid at all:

$$RCH_2NO_2 + HONO \longrightarrow R \cdot C\begin{matrix}\nearrow NO_2 \\ \searrow NOH\end{matrix} + H_2O;$$

$$R_2CHNO_2 + HONO \longrightarrow R_2 \cdot C\begin{matrix}\nearrow NO_2 \\ \searrow NO\end{matrix} + H_2O.$$

Salts of nitrolic acids display an isomerism that has not been fully explained. With sodium hydroxide they yield unstable colorless salts,

$$R \cdot C\begin{matrix}\nearrow NO_2 \\ \searrow NONa\end{matrix},$$

which undergo some kind of rearrangement, giving rise to highly colored (usually red) isomers. On exposure to sunlight the red salts become colorless but not identical with the first neutralization products.

ALIPHATIC AMINES

The aliphatic amines are derivatives of ammonia in which hydrogen has been replaced by alkyl radicals. They are classified as primary, secondary, or tertiary, according to the number of hydrogen atoms replaced.

The simplest member of the class, methyl amine, CH_3NH_2, was the first one discovered. It was isolated by Würtz in 1848 from the hydrolysis products of methyl isocyanate. The isocyanate was boiled with potassium hydroxide solution and the amine was released as a gas:

$$CH_3NCO + 2KOH \longrightarrow CH_3NH_2 + K_2CO_3.$$

It has an odor similar to that of ammonia, is very soluble in water (1150 : 1, at 12° C.), and, like ammonia, its solution in water is basic.

An equilibrium exists between ammonia and ammonium hydroxide in aqueous solution:

$$NH_3 + H_2O \rightleftharpoons NH_4OH.$$

The ammonium hydroxide ionizes, yielding hydroxide ions, and by virtue of this ionization it precipitates iron and aluminum as hydroxides from solutions containing ions of these metals. The amines behave in the same way. They turn litmus blue and precipitate the hydroxides of iron and aluminum from aqueous solutions, due to the establishment of the following equilibria:

$$RNH_2 + H_2O \longrightarrow RNH_3OH;$$
$$RNH_3OH \longrightarrow RNH_3^+ + OH^-.$$

Methyl amine is so much like ammonia in all of its chemical and physical properties that it was mistaken for ammonia when first produced and was identified as a different substance only after the observation was made that it burns in air.

Preparation. 1. The amines may be prepared by heating, in sealed tubes, mixtures of alkyl halides and alcoholic solutions of ammonia (Hofmann's method):

$$RX + NH_3 \longrightarrow RNH_2 + HX.$$

Secondary, as well as primary, alkyl halides may be used in this reaction. Mixtures of tertiary alkyl halides and ammonia yield unsaturated hydrocarbons and ammonium salts. Primary and secondary alkyl halides yield olefines when warmed with alcoholic potash but do not ordinarily decompose in this manner in the presence of an excess of ammonia.

The product, RNH_2, is called a primary amine. It is ammonia in which only one hydrogen has been replaced by an alkyl radical. The reaction does not stop, however, when one hydrogen atom of the ammonia molecule has been replaced. Another alkyl halide molecule reacts with the primary amine, replacing one more hydrogen atom with the formation of a secondary amine, R_2NH. This in turn yields a tertiary amine, R_3N, in which the three hydrogen atoms of ammonia have all been replaced by alkyl groups.

Ammonia forms salts with acids by direct addition:

$$NH_3 + HX \longrightarrow NH_4X.$$

Amines form salts in the same way:

$$RNH_2 + HX \longrightarrow RNH_3X.$$

The formulas of the amine salts* are usually written $RNH_2 \cdot HX$, $R_2NH \cdot HX$, and $R_3N \cdot HX$.

From a tertiary amine a quaternary ammonium salt is formed by addition of an alkyl halide:

$$R_3N + RX \longrightarrow R_4NX.$$

The Hofmann method leads to the formation of a mixture of primary, secondary, and tertiary amines, together with quaternary ammonium salts.

Various methods have been devised for isolating pure amines from the mixture. Most of these methods involve the decomposition and loss of at least one of the products. The first step in the separation is accomplished by distilling the alkaline solution with steam. The quaternary ammonium salt, R_4NX, is non-volatile and remains in the distilling flask. The free primary, secondary, and tertiary amines pass over with steam. Nitrous acid acts upon the distillate, converting the primary

* It is illogical to write the formulas in this fashion, for we never represent the corresponding ammonium salts by the formula $NH_3 \cdot HX$.

amine into an alcohol, forming a nitroso compound with the secondary amine and a salt with tertiary compound:

$$CH_3NH_2 + HONO \longrightarrow CH_3OH + H_2O + N_2;$$
$$(CH_3)_2NH + HONO \longrightarrow (CH_3)_2N \cdot NO + H_2O;$$
$$(CH_3)_3N + HONO \longrightarrow (CH_3)_3N \cdot HNO_2.$$

Steam distillation of this mixture in dilute sulphuric acid solution removes the alcohol and nitroso compound, leaving a sulphate of the tertiary amine in the distilling flask. The free tertiary amine is liberated by means of a base and is obtained pure by distilling. The nitroso derivative of the secondary amine usually separates as a yellow oily layer from which the amine can be obtained by boiling it with a strong acid, the original reaction being reversed by the elimination of nitrous acid at the higher temperature:

$$(CH_3)_2N \cdot NO + HOH \longrightarrow (CH_3)_2NH + HNO_2.$$

The primary amine is lost, having been converted into an alcohol, from which it is not easily regenerated.

The most satisfactory general method for separating primary, secondary, and tertiary amines without loss depends upon their reactions with benzenesulphonyl chloride, $C_6H_5SO_2Cl$. This reagent is a colorless liquid which fumes when exposed to moist air. It is prepared from benzene sulphonic acid by the action of phosphorus pentachloride. The mixed amines, separated from the quaternary salts as indicated above, are treated with benzenesulphonyl chloride and potassium hydroxide solution. Primary amines yield products which are soluble in the alkali. Secondary amines yield insoluble products and the tertiary compounds are unchanged: *

$$CH_3NH_2 + C_6H_5SO_2Cl \longrightarrow \underset{\text{(Soluble in alkali)}}{CH_3NHSO_2C_6H_5} + HCl;$$
$$(CH_3)_2NH + C_6H_5SO_2Cl \longrightarrow \underset{\text{(Insoluble in alkali)}}{(CH_3)_2NSO_2C_6H_5} + HCl.$$

The free primary and secondary amines may be recovered from these derivatives by boiling with hydrochloric or sulphuric acid: †

$$CH_3 \cdot NH \cdot SO_2C_6H_5 + HOH \longrightarrow CH_3NH_2 + C_6H_5SO_3H.$$

* Trimethylamine forms a salt with benzenesulphonyl chloride. Vorlander and Nolte, *Ber.*, **46**, 3212 (1913).

† Hinsberg, *Ber.*, **38**, 906 (1905).

2. Primary amines may be prepared free from secondary and tertiary compounds by reduction of nitriles with hydrogen in the presence of finely divided platinum at 200° or by the action of sodium on an alcoholic solution of the nitrile:

$$RCN + 2H_2 \longrightarrow R \cdot CH_2 \cdot NH_2.$$

Nitriles may be regenerated from amines by the action of an excess of bromine:

$$R \cdot CH_2 \cdot NH_2 + 2Br_2 \longrightarrow RCN + 4HBr.$$

3. Amines are formed through the reduction of nitro-paraffins by sodium amalgam in alcohol or by zinc or tin in hydrochloric acid:

$$RNO_2 + 3H_2 \longrightarrow RNH_2 + 2H_2O.$$

This method is of little importance in the preparation of aliphatic amines, but constitutes the best method for making the corresponding aromatic compounds. Products that are intermediate between the nitro-paraffin and the amine may be isolated if the reduction is carried out in neutral solution. Thus, nitroethane, when shaken with zinc dust in water, yields nitrosoethane which immediately rearranges to acetaldoxime and the latter is reduced to ethylhydroxylamine:

$$\underset{\text{Nitroethane}}{CH_3 \cdot CH_2 \cdot NO_2} \xrightarrow{H_2} \underset{\text{Nitrosoethane}}{CH_3 \cdot CH_2 \cdot NO} \longrightarrow \underset{\text{Acetaldoxime}}{CH_3 \cdot CH : NOH};$$

$$\underset{\text{Acetaldoxime}}{CH_3 \cdot CH : NOH} \xrightarrow{H_2} \underset{\text{Ethyl hydroxylamine}}{CH_3 \cdot CH_2 \cdot NHOH.}$$

4. Amines are formed when isocyanates are hydrolyzed by boiling with dilute alkali:

$$RNCO + H_2O \longrightarrow RNH_2 + CO_2.$$

5. The action of bromine and an alkali on an acid amide results in the formation of an amine. The net result of the reaction is indicated by the equation given below, but consideration of the mechanism by which it is accomplished is reserved for later treatment.

$$RCONH_2 + 2Br_2 + 4KOH \longrightarrow RNH_2 + 2KBr + K_2CO_3 + 2H_2O.$$

6. The best general method for preparing a pure primary amine is based upon Gabriel's phthalimide reaction. Potassium phthalimide, $C_6H_4(CO)_2NK$, combines with alkyl halides as follows:

$$C_6H_4(CO)_2NK + RX \longrightarrow C_6H_4(CO)_2NR + KX.$$

The product when hydrolyzed yields phtalic acid and a primary amine:

$$C_6H_4(CO)_2NR + 2H_2O \longrightarrow C_6H_4(COOH)_2 + RNH_2.$$

The details of this process are outlined on page 435.

Trimethylamine is prepared by heating a mixture of formaldehyde and ammonium chloride:

$$9CH_2O + 2NH_4Cl \longrightarrow 2(CH_3)_3N \cdot HCl + 3H_2O + 3CO_2.$$

Properties. The amines of low molecular weight are gases, the intermediate members are liquids, and those of high molecular weight are solids. Volatility and solubility decrease as the molecular weights increase. It has been reported by some investigators that they become stronger bases as the number of alkyl radicals substituted for the hydrogen of ammonia increases, but this is denied by Werner,* who found that dimethylamine liberates trimethylamine from its salts in spite of the fact that the former is more volatile than the tertiary base. The quaternary ammonium bases are as strong (highly ionized) as sodium and potassium hydroxides.

The hydrates of the primary, secondary, and tertiary amines act like weak bases, for, like ammonium hydroxide, they lose water and exist largely in the form of free amines in aqueous solution. The quaternary bases cannot lose water, for in these compounds there is no hydrogen attached to the nitrogen atom.

The quaternary compounds are decomposed by heat as follows:

A halogen salt, R_4NX, yields a tertiary amine, R_3N, and an alkyl halide, RX, the latter containing the smallest of the four groups attached to nitrogen.

A quaternary base, R_4NOH, yields a tertiary amine, water, and an unsaturated hydrocarbon: the latter being derived from the largest alkyl radical attached to the nitrogen. But

* Werner, *J. Chem. Soc.*, **113**, 899 (1918).

if no larger group than methyl be present, then the products consist of a tertiary amine and methyl alcohol.

The halogen acid salts of amines are decomposed at high temperatures with the production of alkyl halides.

$$R_3N \cdot HCl \longrightarrow R_2NH + RCl$$
$$R_2NH \cdot HCl \longrightarrow RNH_2 + RCl$$
$$RNH_2 \cdot HCl \longrightarrow NH_3 + RCl.$$

A commercial process for making methyl chloride from trimethyl amine is based upon this reaction.

The primary and secondary amines react with acid chlorides as do the alcohols:

$$RNH_2 + CH_3 \cdot COCl \longrightarrow R \cdot NH \cdot CO \cdot CH_3 + HCl;$$
$$R_2NH + CH_3 \cdot COCl \longrightarrow R_2N \cdot CO \cdot CH_3 + HCl.$$

In some cases both hydrogen atoms in the primary amino group are replaced by acyl radicals; but usually only one is removed, as indicated in the equation. The products (substituted amides) are easily crystallized and purified, and, therefore, readily identified. The reaction is used to establish the identity of unknown amines.

The boiling points of a few amines are given below:

Amine	Mono	Di	Tri
Methyl	−7°	7°	3.5°
Ethyl	19°	56°	90°
n-propyl	49°	110°	156°
isopropyl	32°	84°	
n-butyl	78°	160°	216.5°
isobutyl	66°	136°	187°
secondary butyl	63°	132°	
tertiary butyl	44°		
n-amyl	104°		
isoamyl	95°	187°	235°

Optical activity is exhibited by compounds of pentavalent nitrogen if the five atoms or groups associated with the nitrogen are all different; and by compounds having two groups alike if one of the two similar groups constitutes the negative ion of the quaternary derivative. This lends support to the view that the negative ion is not directly attached to the nitrogen atom. There is, in fact, no necessity for assuming that nitro-

gen is ever directly attached to more than four atoms, and four different atoms or groups attached to any element establish asymmetry and give rise to optical isomers.

Nitrogen, belonging to the fifth group in the periodic system, has five electrons in its outer shell. The core of the atom has an equal positive charge. The valence of nitrogen is satisfied when an octet of electrons is formed around it, and this is accomplished when four atoms are bound to nitrogen by four pairs of electrons. The fifth element or group has no direct attachment to the nitrogen. It acquires from the nitrogen one electron and is held in the neighborhood of the positive ammonium radical without definite orientation. The formulas of ammonium hydroxide and a quaternary ammonium halide may be written as follows:

$$\left[\begin{array}{c} H \\ \circ\circ \\ H:N:H \\ \circ\circ \\ H \end{array}\right] \begin{array}{c} \circ\circ \\ :O:H \\ \circ\circ \end{array} \quad \text{and} \quad \left[\begin{array}{c} R \\ \circ\circ \\ R:N:R \\ \circ\circ \\ R \end{array}\right] \begin{array}{c} \circ\circ \\ :X: \\ \circ\circ \end{array}$$

ALDEHYDES AND KETONES

Primary alcohols are converted by oxidation into aldehydes without loss of carbon. The aldehyde molecule differs in composition from the corresponding alcohol by two hydrogen atoms:

$$\underset{\text{Alcohol}}{C_2H_6O} + \tfrac{1}{2}\,O_2 \longrightarrow \underset{\text{Aldehyde}}{C_2H_4O} + H_2O.$$

The properties of alcohols that depend upon the hydroxyl group are lacking in aldehydes. They contain no hydrogen that is replaceable by metals. They are readily reduced by alkali metals. Phosphorus pentachloride acts upon the aldehyde molecule, replacing oxygen only, and for each atom of oxygen removed two atoms of chlorine are introduced:

$$C_2H_4O + PCl_5 \longrightarrow C_2H_4Cl_2 + POCl_3.$$

Evidently the hydroxyl hydrogen of the alcohol is one of the two atoms removed by oxidation. The $—CH_2OH$ group is thus converted into $—C\begin{matrix}\diagup H\\ \diagdown\!\!\diagdown O\end{matrix}$:

$$CH_3\cdot CH_2OH \longrightarrow CH_3\cdot C\begin{matrix}\diagup H\\ \diagdown\!\!\diagdown O\end{matrix} + H_2O.$$

The same thing happens in the formation of ketones from secondary alcohols; the group $—CHOH—$ is converted into $—CO—$. Aldehydes and ketones have in common the group $>C{=}O$, known as the carbonyl group. In ketones two valence bonds of the carbonyl group are attached to carbon radicals. In aldehydes one bond is attached to hydrogen and (except in the case of formaldehyde) the other is held by a carbon radical. The general formulas are:

$$\underset{\text{Aldehyde}}{R—C\begin{matrix}\diagup H\\ \diagdown\!\!\diagdown O\end{matrix}} \quad \text{and} \quad \underset{\text{Ketone}}{\begin{matrix}R\diagdown\\ R'\diagup\end{matrix}C{=}O.}$$

Nomenclature. The aldehydes are named from the acids which they produce when oxidized. Formaldehyde or formic

aldehyde, $H \cdot CHO$, is the member of the series from which formic acid may be derived. Acetaldehyde or acetic aldehyde, $CH_3 \cdot CHO$, yields acetic acid.

Ketones are named from the radicals attached to the carbonyl group. Thus $CH_3 \cdot CO \cdot CH_3$ is dimethyl ketone, and $CH_3 \cdot CO \cdot CH(CH_3)_2$ is methyl-isopropyl ketone.

According to the Geneva system an aldehyde is named from the hydrocarbon having the same number of carbon atoms. The final *e* of the hydrocarbon name is changed to *al* to indicate the presence of the aldehyde group. Thus $H \cdot CHO$ is methanal, $CH_3 \cdot CHO$ is ethanal, and so on. A ketone is named by changing the final *e* of the name of the corresponding hydrocarbon to *one*. A number following the name indicates the position of the carbonyl group, for example, $CH_3 \cdot CH_2 \cdot CO \cdot CH_2 \cdot CH_3$ is pentanone-3 and $CH_3 \cdot CH_2 \cdot CH_2 \cdot \underset{\displaystyle CH_3}{\underset{|}{CH}} \cdot CO \cdot CH_3$ is 4-methyl-hexanone-5 or 3-methyl-hexanone-2.

ALDEHYDES

Name	Formula	M.P.	B.P.	Sp. Gr.
Formaldehyde	$HCHO$	−92°	−21°	0.815(−20°)
Acetaldehyde	CH_3CHO	−120°	20.8°	0.780(20°)
Propionaldehyde	C_2H_5CHO	−81°	49°	0.708(20°)
n-Butyraldehyde	C_3H_7CHO	−99°	74°	0.817(20°)
Isobutyraldehyde	C_3H_7CHO	−65.9°	63°	0.794(20°)
n-Valeraldehyde	C_4H_9CHO		103°	0.819(11°)
Isovaleraldehyde	C_4H_9CHO	−51°	92°	0.798(20°)
Trimethylacetaldehyde . . .	C_4H_9CHO	+3°	75°	0.793(18°)
Undecanaldehyde	$C_{10}H_{21}CHO$	−4°	117°	0.825(23°)

KETONES

Name	Formula	M.P.	B.P.	Sp. Gr.
Acetone	CH_3COCH_3	−93.9°	56.3°	0.797(20°)
Methylethyl ketone	$CH_3COC_2H_5$	−85.9°	78.6°	0.816(20°)
Diethyl ketone	$C_2H_5COC_2H_5$	−42°	101°	0.821(15°)
Methylpropyl ketone	$CH_3COC_3H_7$	−77.8°	101.8°	0.808(20°)
Dipropyl ketone	$C_3H_7COC_3H_7$	−32.6°	144°	0.820(20°)
Diisopropyl ketone	$C_3H_7COC_3H_7$		125°	0.825(17°)
Dipentyl ketone	$C_5H_{11}COC_5H_{11}$	15°	227°	0.826(20°)
Dihexyl ketone	$C_6H_{13}COC_6H_{13}$	30.5°	264°	0.825(30°)
Methylhexyl ketone	$CH_3COC_6H_{13}$	−16°	173°	0.820(16°)
Methyloctyl ketone	$CH_3COC_8H_{17}$	3.5°	211°	0.825(20°)

Preparation. Aldehydes and ketones may be prepared by the following methods:

1. Dry distillation of salts of organic acids:

$$\underset{\text{Sodium acetate}}{2CH_3 \cdot COONa} \longrightarrow \underset{\text{Acetone}}{CH_3 \cdot CO \cdot CH_3} + Na_2CO_3; \qquad (1)$$

$$\underset{\text{Sodium acetate}}{CH_3 \cdot COONa} + \underset{\text{Sodium proprionate}}{C_2H_5 \cdot COONa} \rightarrow \underset{\text{Methylethyl ketone}}{CH_3 \cdot CO \cdot C_2H_5} + Na_2CO_3. \qquad (2)$$

Mixed products are obtained from reactions of mixed salts, for a ketone may be formed from any two salt molecules. In addition to methylethyl ketone, formed as indicated in equation 2, the same mixture of salts yields dimethyl ketone and diethyl ketone. A mixture of a formate with a salt of another organic acid may be distilled to produce an aldehyde:

$$H \cdot COONa + CH_3 \cdot COONa \longrightarrow CH_3 \cdot CHO + Na_2CO_3.$$

Formaldehyde and acetone are by-products in this reaction.

2. Oxidation of an alcohol by means of potassium dichromate and sulphuric acid, or by an acid or alkaline solution of potassium permanganate. Secondary alcohols yield ketones:

$$CH_3 \cdot CHOH \cdot CH_3 \longrightarrow CH_3 \cdot CO \cdot CH_3 + H_2O.$$

Primary alcohols yield aldehydes:

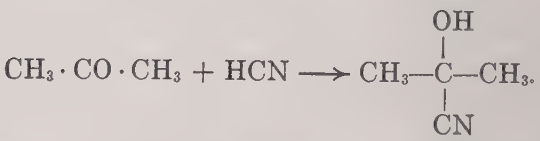
$$CH_3 \cdot CH_2OH \longrightarrow CH_3 \cdot CHO + H_2O.$$

The reactions of aldehydes and ketones depend upon the activity of the carbonyl group. Acetaldehyde, $CH_3 \cdot CHO$, and acetone, $CH_3 \cdot CO \cdot CH_3$, may be considered as typical representatives of the two classes, and the formulas of these compounds are used in the equations which represent the following general reactions:

I. ADDITION REACTIONS

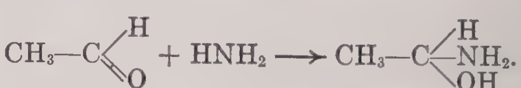
Many reagents form addition products with aldehydes and ketones by breaking the double bond between carbon and oxygen in the carbonyl group. The negative radical of the reagent attaches to the carbon and the positive atom or group combines with the oxygen of the carbonyl group.

a. Hydrocyanic acid. A cyanhydrin is formed by the direct addition of hydrogen cyanide to an aldehyde or ketone.



This reaction is important, for it affords a means of introducing a new carbon atom into the molecule. The addition product may be used in the synthesis of other classes of compounds. The —CN group is easily hydrolyzed to —COOH, giving rise to an acid, or it may be reduced to —CH_2NH_2, yielding an amine.

b. Ammonia. Ammonia combines with aldehydes, forming addition products analogous to the compounds formed by addition of hydrocyanic acid. The procedure, in the case of volatile aldehydes, is to pass the vapor, mixed with ammonia gas, into cold ether. The aldehyde ammonia is precipitated in crystalline form:



Aldehyde ammonia

The aldehyde may be regenerated by warming the addition compound with an acid. The reaction is often employed as a means of purifying aldehydes. Very few ketones form addition products with ammonia, and formaldehyde is exceptional in its behavior with this reagent, forming a basic substance known as hexamethylenetetramine:

$$6H \cdot CHO + 4NH_3 \longrightarrow (CH_2)_6N_4 + 6H_2O.$$

c. The Grignard reagent. Magnesium dissolves in an ether solution of an alkyl halide forming an alkyl magnesium compound, RMgX, commonly called the Grignard reagent. (See the chapter on the Grignard reaction.) Alkyl magnesium halides form, with aldehydes and ketones, addition products which may be hydrolyzed to produce alcohols. In this way, form-

aldehyde may be used in the preparation of a primary alcohol. Any other aldehyde gives rise to a secondary alcohol, and ketones are converted into tertiary alcohols:

$$\underset{\text{Formaldehyde}}{H\cdot CHO} + RMgX \longrightarrow H\cdot C\!\!\begin{array}{l}\diagup H\\ -OMgX,\\ \diagdown R\end{array}$$

$$H\cdot C\!\!\begin{array}{l}\diagup H\\ -OMgX\\ \diagdown R\end{array} + HOH \longrightarrow \underset{\text{Primary alcohol}}{R\cdot CH_2OH} + MgXOH.$$

$$\underset{\text{Acetaldehyde}}{CH_3\cdot CHO} + RMgX \longrightarrow CH_3\cdot C\!\!\begin{array}{l}\diagup H\\ -OMgX,\\ \diagdown R\end{array}$$

$$CH_3\cdot C\!\!\begin{array}{l}\diagup H\\ -OMgX\\ \diagdown R\end{array} + HOH \longrightarrow \underset{\text{Secondary alcohol}}{CH_3\cdot C\!\!\begin{array}{l}\diagup H\\ -OH\\ \diagdown R\end{array}} + MgXOH.$$

$$\underset{\text{Acetone}}{\begin{array}{l}CH_3\diagdown\\ CH_3\diagup\end{array}\!\!C:O} + RMgX \longrightarrow \begin{array}{l}CH_3\diagdown\\ CH_3\diagup\end{array}\!\!C\!\!\begin{array}{l}\diagup OMgX\\ \diagdown R\end{array},$$

$$\begin{array}{l}CH_3\diagdown\\ CH_3\diagup\end{array}\!\!C\!\!\begin{array}{l}\diagup OMgX\\ \diagdown R\end{array} + HOH \longrightarrow \underset{\text{Tertiary alcohol}}{\begin{array}{l}CH_3\diagdown\\ CH_3\diagup\end{array}\!\!C\!\!\begin{array}{l}\diagup OH\\ \diagdown R\end{array}} + MgXOH.$$

d. Bisulphites. Sodium hydrogen sulphite forms a crystalline addition product with aldehydes and with many ketones:

$$CH_3\cdot CHO + NaHSO_3 \longrightarrow CH_3\cdot C\!\!\begin{array}{l}\diagup H\\ -OH\\ \diagdown SO_3Na\end{array}$$

This reaction furnishes a convenient method for separating these compounds from alcohols and acids with which they are often contaminated. After washing the solid addition product, it is distilled with sodium carbonate, and the original aldehyde or ketone is liberated.

e. Acylhalides. Aldehydes react with acid chlorides and bromides, forming halogenated esters*:

$$\underset{\text{Formaldehyde}}{H\cdot CHO} + \underset{\text{Acetyl chloride}}{CH_3\cdot COCl} \longrightarrow \underset{\text{Chlormethyl acetate (b.p. 115°)}}{H\cdot C\!\!\begin{array}{l}\diagup H\\ -O\cdot CO\cdot CH_3.\\ \diagdown Cl\end{array}}$$

* Adams and Ulrich, *J. Am. Chem. Soc.*, **43**, 660 (1921).

Esters of this type react with ammonia, forming amides, ammonium chloride, and the original aldehydes. With primary and secondary aliphatic amines they yield substituted amides, amine hydrochlorides, and aldehydes:

$$H\cdot C\begin{array}{l}\diagup H\\ -O\cdot CO\cdot CH_3\\ \diagdown Cl\end{array} + RNH_2 \longrightarrow HCHO + RNH\cdot CO\cdot CH_3 + HCl.$$

*f. Aldol condensation.** In the presence of zinc chloride or sodium acetate, or in alkaline solution, acetaldehyde condenses to form a compound having twice the molecular weight of the original aldehyde. The compound consists of two aldehyde molecules, chemically combined, and is known as aldol. The reaction involved is similar to the addition of HCN or $NaHSO_4$. Hydrogen attaches to the carbonyl oxygen, and the residue of the molecule becomes attached to carbon:

$$CH_3-C\begin{array}{l}\diagup\!\!\diagup O\\ \diagdown H\end{array} + CH_3\cdot CHO \longrightarrow \underset{\text{Aldol}}{CH_3-C\begin{array}{l}\diagup OH\\ -CH_2-CHO.\\ \diagdown H\end{array}}$$

Similar condensations of other aldehydes have been induced, in some cases six or more molecules combining. Invariably it is hydrogen on the α-carbon atom, that is, on the carbon atom adjacent to the —CHO group, which takes part in the reaction. Thus propionaldehyde molecules condense as follows:

$$CH_3\cdot CH_2\cdot CHO + CH_3\cdot CH_2\cdot CHO \longrightarrow CH_3\cdot CH_2\cdot CHOH\cdot \underset{\displaystyle CH_3}{\underset{|}{CH}}\cdot CHO.$$

II. REDUCTION

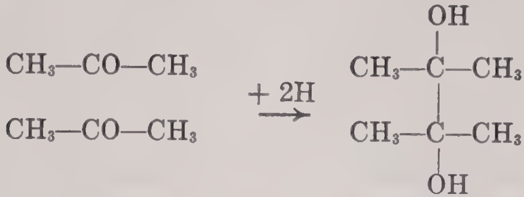
Sodium amalgam or any source of nascent hydrogen reduces aldehydes and ketones with the formation of alcohols:

$$CH_3\cdot CHO + 2H \longrightarrow CH_3\cdot CH_2OH;$$
$$CH_3\cdot CO\cdot CH_3 + 2H \longrightarrow CH_3\cdot CHOH\cdot CH_3.$$

Ditertiary alcohols, pinacols, are formed also in the reduction

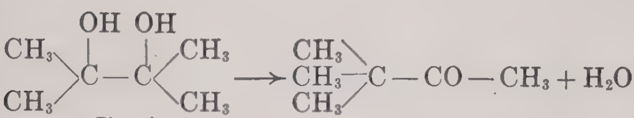
* Condensation is a term applied to a variety of reactions in which two or more molecules, alike or different, unite by the linking of carbon atoms with or without the elimination of water.

of ketones, but as a rule the secondary alcohol is the chief product.



Acetone Tetramethyl pinacol

This pinacol is a crystalline solid, melting at 38°. It effloresces on exposure to air. When warmed with sulphuric acid, it undergoes an intramolecular rearrangement in which it loses a molecule of water and forms pinacolone or tertiarybutylmethyl ketone.



Pinacol Pinacolone

III. OXIDATION

a. On oxidation aldehydes yield acids without loss of carbon, but ketones yield either carbon dioxide and water or acids containing fewer carbon atoms than in the original ketone; the products formed depend upon the nature of the ketone, the vigor of the oxidizing agent, the temperature, concentration, the solvent used, and other factors.

$$\underset{\text{Acetaldehyde}}{CH_3 \cdot CHO} + O \longrightarrow \underset{\text{Acetic acid}}{CH_3 \cdot COOH};$$

$$\underset{\text{Acetone}}{CH_3 \cdot CO \cdot CH_3} + 4O \longrightarrow \underset{\text{Acetic acid}}{CH_3 \cdot COOH} + H_2O + CO_2.$$

The first oxidation products of ketones are acids formed by breaking the molecule at the position of the carbonyl group. The ketone $CH_3 \cdot CH_2 \cdot CO \cdot CH_2 \cdot CH\Big\langle\begin{matrix}CH_3\\CH_3\end{matrix}$ yields four acids, namely, $CH_3 \cdot CH_2 \cdot COOH$, $\begin{matrix}CH_3\\CH_3\end{matrix}\Big\rangle CH \cdot COOH$, $CH_3 \cdot COOH$, and $\begin{matrix}CH_3\\CH_3\end{matrix}\Big\rangle CH \cdot CH_2 \cdot COOH$. These products indicate that in

every case the ketone molecule breaks between the carbonyl group and an adjacent carbon; but not always on the same side of the >CO group. The four acids are not produced in equal amounts. The reaction which leaves the carbonyl group attached to the smaller of the two radicals predominates.

b. Fehling's solution. Aliphatic aldehydes and a few ketones are oxidized by an alkaline solution of cupric sulphate. Fehling's solution is made by adding copper sulphate to a solution of sodium potassium tartrate and sodium hydroxide. In the presence of tartrates cupric hydroxide is not precipitated. A clear dark blue solution is formed which, when warmed with an aldehyde, yields a brick-red precipitate of cuprous oxide. In a qualitative way, the change may be represented by the equation:

$$R \cdot CHO + 2Cu(OH)_2 \longrightarrow Cu_2O + 2H_2O + R \cdot COOH.$$

This reaction is of clinical value. It is the test ordinarily applied to determine the presence or absence of glucose in the urine. There is a definite relationship between the amount of cuprous oxide precipitated and the amount of sugar oxidized (a relationship not accurately represented by the above equation), so that the reaction forms the basis of quantitative methods for estimating the sugar present in the urine — a matter of prime importance in the diagnosis and treatment of diabetes.

c. Silver oxide. An ammoniacal solution of silver oxide may be made by precipitating silver oxide from silver nitrate solution by the addition of sodium hydroxide and redissolving the precipitate in dilute ammonium hydroxide. When warmed with an aldehyde in a test tube or beaker, a fine mirror is produced on the walls of the container through the plating out of metallic silver:

$$Ag_2O + RCHO \longrightarrow RCOOH + 2Ag.$$

A few ketones also reduce silver oxide.

IV. REACTIONS INVOLVING REMOVAL OF THE CARBONYL OXYGEN

a. Phosphorus pentachloride acts upon aldehydes and ketones, replacing the carbonyl oxygen by two chlorine atoms:

$$CH_3 \cdot CHO + PCl_5 \longrightarrow CH_3 \cdot CHCl_2 + POCl_3;$$
$$CH_3 \cdot CO \cdot CH_3 + PCl_5 \longrightarrow CH_3 \cdot CCl_2 \cdot CH_3 + POCl_3.$$

b. Hydroxylamine reacts with aldehydes and ketones, eliminating water and forming oximes:

$$CH_3\cdot CHO + H_2NOH \longrightarrow \underset{\text{Acetaldoxime}}{CH_3\cdot CH:NOH} + H_2O;$$

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>C:O + H_2NOH \longrightarrow \underset{\text{Dimethyl ketoxime}}{\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>C:NOH} + H_2O.$$

The oximes are readily changed by intramolecular rearrangement into totally different compounds. The change is discussed under "The Beckmann Rearrangement."

c. With aldehydes and ketones, phenylhydrazine and its derivatives form compounds known as hydrazones:

$$CH_3\cdot CHO + H_2N\cdot NH\cdot C_6H_5 \longrightarrow CH_3\cdot CH:N\cdot NH\cdot C_6H_5 + H_2O;$$

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>C:O + H_2N\cdot NH\cdot C_6H_5 \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>C:N\cdot NH\cdot C_6H_5 + H_2O.$$

Hydrazones are hydrolyzed by boiling with acids, the original aldehyde or ketone being regenerated. Precipitation and purification of a hydrazone and subsequent hydrolysis afford a means of purifying these bodies.

V. OTHER REACTIONS

a. When aldehyde and alcohol mixtures are saturated with hydrogen chloride gas and heated under pressure, acetals are formed:

$$CH_3\cdot CHO + 2C_2H_5OH \longrightarrow \underset{\text{Acetal}}{CH_3\cdot CH(OC_2H_5)_2} + H_2O.$$

The lower members of the series of acetals are volatile liquids of aromatic odor. They are less dense than water and quite stable. They dissolve in alcohol and in ether; but are almost insoluble in water. When digested for a long time with dilute hydrochloric acid at 100°, they are hydrolyzed, the aldehydes and alcohols being regenerated.

b. Magenta, a beautiful red dye, is decolorized by sulphur dioxide. A few drops of an aldehyde solution promptly restores the color. The composition of the reaction product has not been definitely established.

FORMALDEHYDE

Formaldehyde, HCHO, is a gas under ordinary conditions of temperature and pressure. It has an irritating effect upon the mucous membrane, causes suffocation and produces tears. Most aldehydes resinify when warmed with concentrated alkalies. The behavior of formaldehyde in alkaline solution is exceptional. Instead of forming a resin it undergoes an inter-molecular oxidation and reduction, forming methyl alcohol and formic acid:

$$2HCHO + H_2O \longrightarrow CH_3OH + HCOOH.$$

Formaldehyde is soluble in water and is usually placed on the market in the form of an aqueous solution (formalin, 40 per cent HCHO) or as "paraform," a wax like solid polymer of formaldehyde. The tendency of formaldehyde to polymerize, that is, for two or more molecules to unite with each other, is so pronounced that evaporation of formalin on a steam bath results in the formation of a large amount of paraform or oxymethylene $(CH_2O)n$. This solid substance decomposes when heated, yielding formaldehyde gas. It is used in the manufacture of candles which on burning release the gas in sufficient quantities to serve for fumigation. The pure gas liquefies at $-21°$, and on standing the liquid polymerizes. However, it is possible to secure crystals of pure formaldehyde by rapidly cooling it to $-92°$ by means of liquid air. The crystals are soluble in cold ether. The molecular weight of formaldehyde in the vapor phase corresponds to the formula CH_2O. In solution it varies with the concentration. In concentrated solutions the dissolved molecules associate, forming aggregates consisting of double or triple molecules. There is also evidence of hydration, the single, double, and triple molecules of the aldehyde uniting with the solvent to form heavier molecules. A crystalline polymer of definite composition and molecular weight has been isolated from the amorphous mass formed when formalin is evaporated. It is the chief product obtained when anhydrous liquid formaldehyde polymerizes. The compound is known as trioxymethylene. It sublimes unchanged, dissolves in water, and has the formula $(CH_2O)_3$. A different type of condensation of formaldehyde induced by dilute alkalies is mentioned in connection with the formation of acrose.

Formaldehyde is prepared commercially by passing a mixture of air and methyl alcohol vapor over hot copper:

$$CH_3OH + \frac{1}{2}O_2 \longrightarrow HCHO + H_2O.$$

It is used as a germicide. It renders albuminous substances tough and insoluble and is used in large quantities in the preparation of tissues for histological work. It finds employment also in the manufacture of various types of plastics, including artificial ivory from casein, and bakelite from phenol.

A quantitative estimation of formaldehyde may be made by oxidizing it with hydrogen peroxide in the presence of a measured excess of standard sodium hydroxide solution:

$$HCHO + NaOH + H_2O_2 \longrightarrow HCOONa + 2H_2O.$$

The quantity of base used in the reaction is determined by titration and the corresponding quantity of the aldehyde is calculated on the basis of the equation.

Qualitatively formaldehyde may be detected by mixing the solution to be tested with an equal volume of milk and a few drops of ferric chloride. Concentrated sulphuric acid is then carefully introduced so as to form a layer below the mixture. A violet ring at the juncture of the two liquid layers indicates the presence of formaldehyde. A more sensitive test recommended by Schryver is made as follows: To 10 cc. of the solution to be analyzed add 2 cc. of 1 per cent solution of phenylhydrazine hydrochloride (freshly prepared and filtered) 1 cc. of 5 per cent solution of potassium ferricyanide, and 5 cc. of concentrated hydrochloric acid. A red color develops immediately if formaldehyde is present.

ACETALDEHYDE

Acetaldehyde, $CH_3 \cdot CHO$, a colorless, inflammable liquid (m.p. $-120.6°$, b.p. 21°, sp. gr. 0.801), is usually prepared by allowing a mixture of alcohol and sulphuric acid to drop on powdered potassium dichromate.

$$3CH_3 \cdot CH_2OH + Cr_2O_7^{--} + 8H^+ \longrightarrow 2Cr^{+++} + 7H_2O + 3CH_3 \cdot CHO.$$

Conversion of the alcohol to acetic acid is prevented by continuous distillation, the aldehyde being removed as fast as formed. The aldehyde is miscible in all proportions with water, alcohol, and ether. On exposure to air it slowly takes up oxygen, forming acetic acid. In addition to the general methods for preparing aldehydes a few special methods for making acetaldehyde have been employed with success. The aldehyde

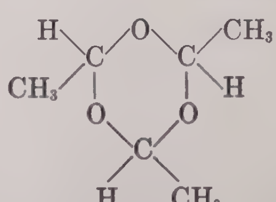
is formed from acetylene by the addition of water. The reaction is actually carried out by treating mercury acetylide and mercurous chloride with dilute hydrochloric acid. Complex intermediate products are formed,* but the net result is expressed by the equation:

$$CH{\equiv}CH + H_2O \longrightarrow CH_3{-}CHO.$$

Ethylene, also, may be used as a source of acetaldehyde. Its oxidation gives rise to glycol, $CH_2OH{-}CH_2OH$, which loses water when warmed with zinc chloride and forms acetaldehyde. The elimination of water probably results in the transient existence of $CH_2:CHOH$; but a hydroxyl group does not, as a rule, remain attached to a doubly linked carbon atom. The hydroxyl hydrogen migrates to the adjacent carbon, leaving, in this case, $CH_3 \cdot CHO$.

At 400° acetaldehyde begins to decompose into methane and carbon monoxide, and at 600° decomposition is rapid, carbon, hydrogen, and water vapor appearing among the products formed.

Acetaldehyde polymerizes very readily. A few drops of concentrated sulphuric acid induce a condensation that proceeds with almost explosive violence. When the action ceases, the acetaldehyde (b.p. 21°) has been converted into a liquid of much greater density and boiling more than 100° higher (b.p. 124°; sp. gr. 0.994). The formula of the new compound, known as paracetaldehyde, is $(C_2H_4O)_3$. It fails to exhibit the ordinary aldehyde reactions. For example, it does not reduce ammoniacal silver solution nor does it resinify with alkalies. On this account it is assumed that the —CHO groups are involved in the union of the three molecules in such a way as to destroy the aldehyde structure. It fails, also, to react with sodium, so that there can be no hydroxyl groups present. The following constitutional formula for paracetaldehyde has been proposed:



* Kothner, *Ber.*, 31, 2475 (1898).

When distilled with dilute sulphuric acid, it reverts to ordinary acetaldehyde. The change is reversible and may be represented by a balanced equation:

$$3CH_3 \cdot CHO \rightleftarrows (C_2H_4O)_3.$$

In the process of distillation the more volatile acetaldehyde escapes. The equilibrium is thereby disturbed in such a way as to promote the decomposition of the paracetaldehyde, and the entire mass gradually dissociates, yielding acetaldehyde.

Acetaldehyde yields a different polymer when cooled to a temperature below zero and treated with hydrogen chloride gas. The condensation product separates in the form of colorless needle-like crystals. On the basis of cryoscopic measurements it has been assigned the formula $(C_2H_4O)_4$. It is called metacetaldehyde. It lacks the characteristic properties of aldehydes, sublimes at 160°, and at 200° passes quantitatively into acetaldehyde. At ordinary temperatures it undergoes a slow partial conversion into acetaldehyde. An equilibrium is established between the three forms:

$$\text{Paracetaldehyde} \rightleftarrows \text{Acetaldehyde} \rightleftarrows \text{Metacetaldehyde}.$$

The condition of equilibrium is influenced by the temperature. Either form may be made to predominate by controlling the conditions of the experiment. The conversion of one polymer into the other seems to be accomplished only through depolymerization followed by a reassociation of the molecules.

The aldol condensation. An entirely different condensation of acetaldehyde, known as the aldol condensation, is induced by dilute alkali, zinc chloride, or sodium acetate. Two molecules unite to form a liquid which retains the aldehyde character and is readily oxidized to hydroxy butyric acid. The change is represented as follows:

$$CH_3\text{—}CHO + CH_3\text{—}CHO \longrightarrow \underset{\text{Aldol}}{CH_3\text{—}CHOH\text{—}CH_2\text{—}CHO}.$$

In this case the union between the two aldehyde molecules is established by linking carbon to carbon (not carbon to oxygen). It is a firm union, and acetaldehyde is not regenerated from aldol by heating nor by any other direct method.

An aldol condensation can be obtained with other aldehydes. The mechanism of the reaction involves a migration of hydrogen from the α-carbon atom in one molecule to aldehyde oxygen in

the other. Thus, propionaldehyde, under the influence of dilute alkali, condenses as follows:

$$CH_3\text{—}CH_2\text{—}CHO + \overset{\beta}{C}H_3\text{—}\overset{\alpha}{C}H_2\text{—}CHO$$

$$\longrightarrow CH_3\text{—}CH_2\text{—}\begin{array}{c}H\\ |\\ C\\ |\\ OH\end{array}\text{—}\begin{array}{c}\\ \\ CH\\ |\\ CH_3\end{array}\text{—}CHO.$$

Aldehydes having no hydrogen attached to the α-carbon do not undergo the aldol condensation. (See p. 429.)

There is some evidence in support of the claim that the first step in an aldol condensation consists of an addition of water to the aldehyde.

$$R\text{—}CH_2\text{—}CHO + H_2O \longrightarrow R\text{—}CH_2\text{—}C\begin{array}{l}\diagup H\\ \text{—}OH\\ \diagdown OH\end{array}$$

The addition product then reacts with an unchanged aldehyde molecule to form an aldol and water.

$$R\text{—}CH_2\text{—}\begin{array}{c}H\\ |\\ C\\ |\\ OH\end{array}\text{—}OH + R\text{—}CH_2\text{—}CHO \longrightarrow R\text{—}CH_2\text{—}\begin{array}{c}H\\ |\\ C\\ |\\ OH\end{array}\text{—}\begin{array}{c}\\ \\ CH\\ |\\ R\end{array}\text{—}CHO.$$

ACETONE

Acetone, $CH_3 \cdot CO \cdot CH_3$, is a colorless liquid with an agreeable odor and burning taste (b.p. 56.3°, m.p. − 93.9°, sp. gr. 0.812). It is obtained by distilling calcium acetate, or it may be produced, along with methyl alcohol, acetic acid, and other products, by distilling wood. Hydroxylamine converts acetone into a crystalline oxime melting at 69°. When distilled with sulphuric acid, water is eliminated and a condensation product, known as mesitylene, is formed:

$$3CH_3 \cdot CO \cdot CH_3 \longrightarrow 3H_2O + C_9H_{12}.$$

In aqueous solution acetone is reduced by sodium amalgam, the principal product being isopropyl alcohol.

Sodium acts upon anhydrous acetone, liberating hydrogen and forming a white powder corresponding to the formula C_3H_5ONa.* In all probability the reaction is due to the existence of an enolic form of acetone. Hydroxyl hydrogen is always easily replaced by sodium:

$$\underset{\text{Keto form}}{CH_3 \cdot CO \cdot CH_3} \rightleftarrows \underset{\text{Enol form}}{CH_3 \cdot COH : CH_2}.$$

* Bacon and Freer, *Am. Chem. J.*, **38**, 367 (1907).

KETENES

Compounds represented by the formula $R_2C:C:O$ are known as ketenes. In many respects they resemble ketones; but the adjacent double bonds confer upon the members of this group some properties not shared by the ordinary ketones. The simplest member of the series, CH_2CO, commonly called ketene, is a colorless poisonous gas which liquifies under atmospheric pressure at $-56°$. It is one of the products formed when acetic anhydride or acetone is passed through a red-hot tube:

$$CH_3 \cdot CO \cdot CH_3 \longrightarrow CH_2:CO + CH_4.$$

Ketenes are classified by Staudinger as aldoketenes if they correspond to the formula $RHC:CO$ and ketoketenes if they have the structure $R_2C:C:O$. The former polymerize so rapidly that it is almost impossible to secure pure samples of the monomolecular forms. They are colorless substances (most of them liquids) having disagreeable odors. The ketoketenes are yellow, red, or green. Both types dissolve unchanged in benzene or ether, but are decomposed by water or alcohol.

The ketenes are highly reactive compounds. Most of them are susceptible to oxidation by the air. They react with water, alcohols, mercaptans, amines, ammonia, acids, halogens, halogen acids, alkyl magnesium halides, and with nascent hydrogen:

$$R_2C:C:O + H_2O \longrightarrow \underset{\text{Acid}}{R_2CH \cdot COOH},$$

$$R_2C:C:O + C_2H_5OH \longrightarrow \underset{\text{Ester}}{R_2CH \cdot COOC_2H_5},$$

$$R_2C:C:O + C_2H_5SH \longrightarrow \underset{\text{Thioester}}{R_2CH \cdot COSC_2H_5},$$

$$R_2C:C:O + R'NH_2 \longrightarrow \underset{\text{Amide}}{R_2CH \cdot CONHR'},$$

$$R_2C:C:O + NH_3 \longrightarrow \underset{\text{Amide}}{R_2CH \cdot CONH_2},$$

$$R_2C:C:O + RCOOH \longrightarrow \underset{\text{Acid anhydride}}{R_2CH \cdot CO \cdot O \cdot CO \cdot R}.$$

$$R_2C:C:O + Br_2 \longrightarrow \underset{\text{Bromacid bromide}}{R_2CBr \cdot COBr},$$

$$R_2C:C:O + HBr \longrightarrow \underset{\text{Acid bromide}}{R_2CH \cdot COBr},$$

$$R_2C:C:O + C_2H_5MgBr \longrightarrow \begin{array}{l} R_2C \cdot CO \cdot C_2H_5 \\ \quad \dot{M}gBr \end{array}$$

$$\begin{array}{l} R_2C \cdot CO \cdot C_2H_5 \\ \dot{M}gBr \end{array} + H_2O \longrightarrow \underset{\text{Ketone}}{R_2CH \cdot CO \cdot C_2H_5} + MgBrOH$$

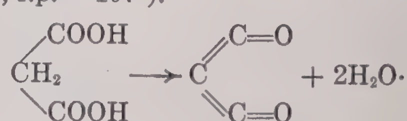
$$R_2C:C:O + H_2 \longrightarrow \underset{\text{Aldehyde}}{R_2CH \cdot CHO}.$$

Preparation. Ketenes are formed by the action of zinc on α-halogenacid chlorides or bromides.

$$CH_3 \cdot CHCl \cdot COCl + Zn \longrightarrow CH_3 \cdot CH:C:O + ZnCl_2.$$

Magnesium and silver have been used instead of zinc; but the former causes loss of material through side reactions and the latter acts very slowly. Anhydrous ether is the solvent ordinarily employed. Bromides are more reactive than chlorides, the latter sometimes failing to respond at all, as in the case of chloracetyl chloride. The character of the substituent on the alpha carbon atom influences the rate of change and the yield of ketene.

Carbon suboxide. When dry malonic acid is heated with ten times its weight of phosphorus pentoxide, a small yield of carbon suboxide (C_3O_2) is obtained. It is a colorless, poisonous gas (b.p. 7°, f.p. −107°).



It is not easy to secure carbon suboxide. The chief products obtained from malonic acid are carbon dioxide and acetic acid. The yield of the suboxide is increased by keeping the pressure below 5 mm. Carbon suboxide is liquified under low pressure by cooling with liquid air. It is a typical ketene.

SATURATED MONOBASIC ACIDS

The saturated monobasic acids may be regarded as derivatives of the paraffin hydrocarbons in which one hydrogen atom has been replaced by the carboxyl group, —COOH. They correspond to the general formula $C_nH_{2n+1}COOH$ or R—COOH.

The lower members of the series are mobile, colorless liquids, having pungent odors and a sour taste. The intermediate members are oily liquids sparingly soluble in water, and those of higher molecular weight are odorless solids insoluble in water, but readily soluble in alcohol, chloroform, or ether. The lower members distill without decomposition. Those of higher molecular weight decompose before boiling. The acids of this series having odd numbers of carbon atoms are rarely found in nature; those having even numbers of carbon atoms are abundant.

The acids of lowest molecular weight have the highest densities, they are the best electrolytes, the most soluble in water, and the most volatile. These qualities are, no doubt, associated with their relatively high per cent of oxygen. As the molecular weights increase the influence of the two oxygen atoms become less marked, and in chemical and physical properties the acids become more like the corresponding hydrocarbons. Formic acid is by far the strongest one of the series.

Representing the equilibrium between the ions and undissociated molecules in aqueous solution by the equation,

$$HAc \rightleftharpoons \overset{+}{H} + \overset{-}{Ac},$$

letting n represent the number of mols of acid dissolved in v liters of water and a the number of mols dissociated when equilibrium is established, we have for the concentration of undissociated molecules the value $\frac{n-a}{v}$. The concentration of each ion is $\frac{a}{v}$ and from the mass law

$$\frac{\left(\frac{a}{v}\right)^2}{\frac{n-a}{v}} = \text{a constant } (k), \text{ or } k = \frac{a^2}{v(n-a)}.$$

Ostwald determined the numerical values of the ionization constants for a large number of saturated acids. The values for $k \times 10^4$ are as follows:

Formic	2.14	Valeric	0.15	Caproic (*n*)	0.14
Acetic	0.18	Isovaleric	0.17	Isobutyl acetic	0.15
Propionic	0.13	Methyl ethyl acetic	0.16	Diethyl acetic	0.20
Butyric	0.15	Trimethyl acetic	0.09	Dimethyl ethyl acetic	0.09

It is obvious that the configuration of the molecule as well as its mass influences the electrolytic dissociation. Negative elements or groups substituted for hydrogen on the carbon atom adjacent to the carboxyl (the α-carbon) greatly enhance the dissociation. Alkyl radicals on the alpha carbon atom generally reduce the strength of the acid. Thus we have the following values for $k \times 10^4$.

Acetic	$CH_3 \cdot COOH$	0.18
Chloracetic	$CH_2Cl \cdot COOH$	15.50
Dichloracetic	$CHCl_2 \cdot COOH$	514.00
Trichloracetic	$CCl_3 \cdot COOH$	12100.00
Cyanacetic	$CH_2CN \cdot COOH$	37.00
Hydroxyacetic	$CH_2OH \cdot COOH$	1.52
Methylacetic	$CH_3CH_2 \cdot COOH$	0.13
Dimethylacetic	$(CH_3)_2CH \cdot COOH$	0.14
Trimethylacetic	$(CH_3)_3C \cdot COOH$	0.09
Ethylacetic	$C_2H_5 \cdot CH_2 \cdot COOH$	0.15

Preparation. 1. The best general method for making the saturated monobasic acids is the oxidation of primary alcohols. Potassium dichromate and sulphuric acid are commonly employed to supply the oxygen required.

$$3R \cdot CH_2OH + 2Cr_2O_7^{--} + 16H^+ \longrightarrow 3R \cdot COOH + 4Cr^{+++} + 11H_2O.$$

2. **Reduction of unsaturated acids.** This is accomplished by means of sodium amalgam or by zinc in acid or alkaline solution or by the action of free hydrogen in the presence of a catalyst such as finely divided nickel or palladium. The reaction is of technical importance in the conversion of oleic acid into stearic acid. Another example is afforded by the conversion of acrylic acid into propionic acid:

$$CH_2 : CH \cdot COOH + H_2 \longrightarrow CH_3 \cdot CH_2 \cdot COOH.$$

3. **Hydrolysis of nitriles.** Alkyl cyanides — the nitriles — are hydrolyzed by boiling with dilute hydrochloric acid:

$$C_2H_5 \cdot CN + 2H_2O \longrightarrow C_2H_5 \cdot COONH_4.$$

Other methods for synthesizing acids are given in the discussions of acetoacetic ester and of malonic ester and in the chapter devoted to the Grignard reaction.

Nomenclature. Special names have been given to all of the common acids, and well-established names, though often meaningless, are not easily replaced by scientific nomenclature. A complete system for naming the acids is based upon the names of the paraffin hydrocarbons having the same number of carbon atoms in the longest continuous chain. The final *e* of the name of the hydrocarbon is changed to *oic*. Thus $CH_3 \cdot COOH$ is ethanoic acid; $CH_3 \cdot CH_2 \cdot COOH$ is propanoic acid, etc. Positions of side chains are indicated by numerals preceding the names of the groups. The carboxyl carbon is usually numbered one. The letters of the Greek alphabet are often used to designate a particular position in the chain. The lettering begins with the carbon atom next to the carboxyl group

$$\begin{array}{l} CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}COOH, \end{array} \qquad \begin{array}{l} CH_3{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}\underset{\displaystyle CH_2{-}CH_3}{\underset{|}{CH}}{-}COOH. \end{array}$$

2-Methyl-propanoic acid
or
α-Methyl-propanoic acid

2-Ethyl-3-methyl-pentanoic acid
or
α-Ethyl-β-methyl-pentanoic acid

Acyl radicals. The univalent residual group that would be left if the hydroxyl in the carboxyl group were eliminated from an acid, is called an acyl radical. Acyl radicals do not exist in the free state, but they are present in many types of acid derivatives. They are named from the corresponding acids by changing the final *ic* to *yl*.

Acids		Acyl Radicals	
Formic	$H \cdot COOH$	Formyl	$H \cdot CO$ —
Acetic	$CH_3 \cdot COOH$	Acetyl	$CH_3 \cdot CO$ —
Propionic	$C_2H_5 \cdot COOH$	Propionyl	$C_2H_5 \cdot CO$ —

FORMIC ACID

Formic acid, $H \cdot COOH$, differs from all other members of the series in being easily oxidized. This is due to the fact that it is an aldehyde as well as an acid, $H{-}C\genfrac{}{}{0pt}{}{\diagup\!\!\!\!\!\diagup O}{\diagdown OH}$. It may be

regarded as hydroxylaldehyde. It is decomposed by concentrated sulphuric acid, slowly when cold but with rapid effervescence at high temperatures, the products being carbon monoxide and water. Many of the salts of formic acid are decomposed by heat. Mercury and silver formates when warmed yield the free metals, carbon dioxide and formic acid; half of the acid being liberated and half oxidized.

$$2HCOOAg \longrightarrow 2Ag + CO_2 + H \cdot COOH.$$

With mercuric formate the change takes place in two stages; mercurous formate being first produced and from that salt free mercury is liberated on further heating.

$$2(H \cdot COO)_2Hg \longrightarrow 2H \cdot COOHg + CO_2 + H \cdot COOH;$$
$$2H \cdot COOHg \longrightarrow 2Hg + CO_2 + H \cdot COOH.$$

When heated to 400°, sodium formate yields hydrogen and sodium oxalate.

$$\begin{matrix} H \cdot COONa \\ \\ H \cdot COONa \end{matrix} \longrightarrow H_2 + \begin{matrix} COONa \\ | \\ COONa \end{matrix}.$$

Formic acid is a colorless liquid with an irritating odor. It produces a burning sensation when in contact with the skin, and unless promptly removed it forms blisters. It forms a constant boiling mixture with water (77.5 per cent acid, b.p. 107.1°) and therefore cannot be freed from water by distillation alone. It occurs in the body fluids of ants and bees. It was first obtained by distilling water containing a large number of ants and its name was derived from this source (L. *formica*).

Formic acid may be prepared by any of the following methods, the first three being the most practical.

1. *Oxidation of methyl alcohol.* Air is mixed with the alcohol vapor and passed through a hot tube containing copper turnings:

$$CH_3OH + O_2 \longrightarrow H \cdot COOH + H_2O.$$

2. At temperatures between 150° and 225° sodium hydroxide absorbs carbon monoxide, forming sodium formate:

$$NaOH + CO \longrightarrow H \cdot COONa.$$

Even at ordinary temperatures this reaction proceeds with a measurable velocity.

3. When heated alone, oxalic acid is decomposed with the formation of water, carbon dioxide, and carbon monoxide. If, however, a glycerine solution of oxalic acid is heated to 120°, the principal products are formic acid and carbon dioxide. At higher temperatures allyl alcohol is produced. The glycerol combines with formic acid, producing an ester known as monoformin, which is hydrolyzed by the water present in the crystals of oxalic acid. The hydrolysis results in the regeneration of glycerol and the liberation of formic acid:

$$\begin{array}{c} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \\ \text{Glycerol} \end{array} + \begin{array}{c} COOH \\ | \\ | \\ | \\ COOH \\ \text{Oxalic acid} \end{array} \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2 \cdot O \cdot CHO \\ \text{Glycerol monoformin} \end{array} + CO_2 + H_2O,$$

$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2 \cdot O \cdot CHO \end{array} + H_2O \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + H \cdot C \begin{array}{l} /\!\!/ O \\ \backslash OH \end{array}.$$

4. Formic acid is produced in the hydrolysis of hydrocyanic acid:

$$HCN + 2H_2O \longrightarrow H \cdot COOH + NH_3.$$

5. Chloroform is decomposed by hot caustic alkali, yielding a formate:

$$CHCl_3 + 4KOH \longrightarrow H \cdot COOK + 3KCl + 2H_2O.$$

ACETIC ACID

Acetic acid, CH_3COOH, as formed in the fermentation of fruit juice, was known to the alchemists of the sixteenth century. It was isolated from other fermentation products by Stahl (1720), and first synthesized by Berzelius in 1814.

The anhydrous acid melts at 16.67° and boils at 118° under 760 m.m. pressure. Below 16° C. the crystalline solid has the appearance of ice and the pure acid is commonly called glacial acetic. A rise of temperature and contraction in volume occurs when water is added to acetic acid, the maximum temperature effect, highest density and maximum viscosity being produced when the solution contains equimolal quantities of the acid and water. This indicates the formation of a hydrate $CH_3 \cdot COOH \cdot H_2O$.

Pure acetic acid and a forty-three per cent solution in water have the same density. The changes in density with dilution are indicated in the following table.

Concentration	Specific Gravity	Concentration	Specific Gravity	Concentration	Specific Gravity
100%	1.055	60%	1.069	30%	1.041
90%	1.071	50%	1.062	20%	1.028
80%	1.075	43%	1.055	10%	1.014
70%	1.073	40%	1.052	0%	1.000

Due to the high molecular freezing point constant for acetic acid (3900) and the low molecular weight of water, a very small quantity of water causes a considerable change in the freezing point of the acid. A freezing-point determination, therefore, constitutes a satisfactory method for estimating the concentration of an acetic acid solution. The effect of dilution on the freezing point is indicated in the following table:

Concentration	Freezing Point	Concentration	Freezing Point	Concentration	Freezing Point
100% . . .	16.67°	92.6% . . .	6.25°	70% . . .	–18.1°
99% . . .	14.80°	89.2% . . .	2.7°	60% . . .	–26.6°
98% . . .	13.25°	87.0% . . .	–0.2°	47% . . .	–19.3°
96.2% . .	10.50°	75.4% . . .	–12.8°	10% . . .	–3.4°

Acetic acid is an excellent solvent for many organic compounds. It dissolves readily in the common organic solvents, and in most solvents it exists in the form of double molecules. This state of aggregation is detected by molecular weight determinations and is known as association. Even in the vapor phase, at temperatures below 150°, the molecular weight is nearly twice as high as that required for the formula CH_3COOH. At temperatures above 200° the molecular weight is normal.

Pure acetic acid is not attacked by chlorine nor bromine in the dark, but in the presence of sunlight substitution products are formed. Chloracetic acid, $CH_2ClCOOH$ (m.p. 63°, b.p. 185–187°), and dichloracetic, $CHCl_2COOH$ (m.p. –4°, b.p. 190°), are usually produced in this way. Trichloracetic acid, CCl_3COOH (m.p. 55°, b.p. 195°), is made by oxidizing chloral hydrate with fuming nitric acid.

Several methods have been developed for manufacturing acetic acid. It is used in large quantities, not only as a laboratory reagent, but as the principal acid component of vinegar.

The most important commercial methods of preparation are the oxidation of ethyl alcohol and the distillation of wood.

Oxidation of alcohol. Large wooden tanks are filled with beechwood shavings inoculated with mother of vinegar (*Bacterium aceti*). Dilute alcohol (6 to 10 per cent) is allowed to percolate through the shavings against a counter current of air. The alcohol is distributed in thin layers over the shavings, exposing large surfaces to the air. The shavings also preserve a porous structure in the tanks, allowing free passages for air and they constitute a suitable home for the growth and propagation of the oxidizing bacteria. The reaction is a simple oxidation:

$$CH_3 \cdot CH_2OH + O_2 \longrightarrow CH_3 \cdot COOH + H_2O.$$

The mixture of alcohol and acetic acid drawn from the bottom of one tank is transferred to the top of a similar tank, and so on until the conversion is nearly complete. The time required is about one week. The dilute acid is concentrated by fractional distillation.

Distillation of wood. Wood is distilled from large iron retorts, the temperature being gradually raised to 450° or 500°. Between 160° and 300° a liquid distillate, pyroligneous acid, is produced. It consists chiefly of water, acetic acid, methyl alcohol, and acetone. After adding lime the volatile liquids are distilled off, leaving a solid residue of calcium acetate. An equivalent quantity of sulphuric acid is then added and the liberated acetic acid is removed by distillation.

BUTYRIC ACID

According to the structure theory two acids corresponding to the formula $C_3H_7 \cdot COOH$ should exist and two are known.

Normal butyric, $CH_3—CH_2—CH_2—COOH$ (b.p. 162°), occurs as an ester in butter and in the free state in rancid butter, in Limburger cheese, and in some secretions of the body, especially in perspiration. It is soluble in water, but separates as an oil when the aqueous solution is saturated with calcium chloride. All soluble fatty acids, except formic and acetic, may be salted out of solution.

Lactic acid, occurring in sour milk, is converted into normal butyric acid by the action of microörganisms found in cheese.

Isobutyric acid, $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH\text{—}COOH$ (b.p. 154°), is found free and combined in many plants but never in very large quantities. It is prepared by hydrolyzing isopropyl cyanide. Isopropyl iodide is the most convenient laboratory source:

$$(CH_3)_2CHI + KCN \longrightarrow (CH_3)_2CH \cdot CN + KI$$

$$(CH_3)_2CHCN + 2H_2O \longrightarrow (CH_3)_2CHCOOH + NH_3.$$

The calcium salt of isobutyric acid is more soluble in hot than in cold water. Normal calcium butyrate is more soluble in cold than in hot water.

HIGHER ACIDS

Palmitic acid, $C_{15}H_{31}COOH$, and stearic acid, $C_{17}H_{35}COOH$, occur together as glycerol esters in the natural fats. They are liberated from the glycerol by boiling the fat with an acid. Their salts are formed when the fat is saponified by boiling with alkalies. These acids are white solids, amorphous and wax-like, as ordinarily prepared, but easily crystallized from alcohol or other organic solvents.

When obtained by hydrolysis of fats, they are mixed with oleic acid — an unsaturated compound belonging to a different series. The liquid, oleic acid, is pressed out of the mixture. Stearic and palmitic acids may be separated by adding magnesium acetate to an alcoholic solution of the mixture. Magnesium stearate precipitates, and from the salt the free acid may be obtained by boiling with hydrochloric acid. The free stearic acid solidifies when cold and floats on the surface of the water.

The great importance of these higher members of the series is indicated in the discussion of esters (p. 109).

Oleic acid may be separated from stearic and palmitic acids by forming the lead salts and extracting the mixed salts with ether. Lead oleate is soluble in ether. The free acid is obtained from the salt by treatment with sulphuric acid.

Palmitic acid, n-hexadecylic acid (m.p. 62°), is usually obtained from olive oil, which is composed, almost exclusively, of

the glycerol esters of palmitic and oleic acids. Myricyl palmitate, $C_{15}H_{31}COOC_{30}H_{61}$, the principal component of beeswax, is another source of this acid. Spermaceti, a white waxy substance found in the head of the sperm whale, is composed chiefly of cetyl palmitate, $C_{15}H_{31}COOC_{16}H_{33}$. Myricyl and cetyl palmitates belong to the class of compounds known as esters. They are hydrolyzed by boiling with an acid, forming the free palmitic acid together with myricyl and cetyl alcohol respectively.

$$C_{15}H_{31}COOC_{30}H_{61} + H_2O \longrightarrow \underset{\text{Palmitic acid}}{C_{15}H_{31}COOH} + \underset{\text{Myricyl alcohol}}{C_{30}H_{61}OH}$$

$$C_{15}H_{31}COOC_{16}H_{33} + H_2O \longrightarrow \underset{\text{Palmitic acid}}{C_{15}H_{31}COOH} + \underset{\text{Cetyl alcohol}}{C_{16}H_{33}OH}$$

Palmitic acid has been synthesized by oxidizing cetyl alcohol.

Stearic acid, *n*-octodecylic acid, melts at 69°. As ordinarily prepared, it is a colorless, soft, amorphous substance. It is not difficult to obtain it in crystalline form by slowly cooling a hot saturated alcoholic solution of the acid.

Stearic acid is a normal or straight chain compound.

Dry distillation of a mixture of salts of stearic and acetic acids results in the formation of margarylmethyl ketone.

$$\begin{array}{l} C_{17}H_{35}COONa \\ CH_3COONa \end{array} \longrightarrow C_{17}H_{35} \cdot CO \cdot CH_3 + Na_2CO_3.$$

On oxidation the ketone yields acetic acid, CH_3COOH, and margaric acid, $C_{16}H_{33}COOH$. This proves that the margaryl radical has the structure $C_{16}H_{33}-CH_2-$. From salts of margaric and acetic acids palmitylmethyl ketone, $C_{16}H_{33} \cdot CO \cdot CH_3$, has been made. When oxidized this ketone yields acetic acid and palmitic acid, $C_{15}H_{31}COOH$, showing that the structure of the palmityl radical is $C_{15}H_{31}-CH_2-$. This process has been continued step by step from stearic acid back to capric acid, $C_9H_{19}COOH$, and the latter has been synthesized from lower members of the acetic acid series. It is known to have a straight chain of carbon atoms, its formula being

$$CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot COOH.$$

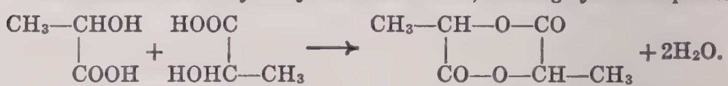
Hence, we know that stearic acid is a straight chain compound having the formula $CH_3 \cdot (CH_2)_{16} \cdot COOH$.

Oleic acid. Although oleic acid, $C_{17}H_{33}COOH$, is not a member of the saturated series, it will be described at this point; for it occurs in the natural fats and oils along with stearic and palmitic acids. It is a colorless, odorless oil which solidifies at 14° and decomposes when distilled under atmospheric pressure.

Oleic acid is a typical unsaturated compound. It forms an addition product with bromine corresponding to the formula $C_{17}H_{33}Br_2COOH$. On oxidation it yields pelargonic acid, $C_8H_{17}COOH$, and azelaic acid, $COOH \cdot (CH_2)_7 \cdot COOH$. Since unsaturated compounds usually break at the position of the double bond, we imply, from this reaction, that the formula of oleic acid is $CH_3 \cdot (CH_2)_7 \cdot CH : CH \cdot (CH_2)_7 \cdot COOH$.

Hydroxy acids. Hydroxy derivatives of the fatty acids are made by reduction of aldehyde acids or ketone acids, by boiling with alkalies the salts of halogen derivatives of the acids, and by other methods.

When heated the α-hydroxy acids lose water, forming cyclic compounds.



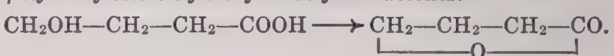
α-Hydroxypropionic acid — Lactide

Under similar treatment β-hydroxy acids form unsaturated acids.

$$CH_3{-}CHOH{-}CH_2{-}COOH \longrightarrow CH_3{-}CH{=}CH{-}COOH + H_2O.$$

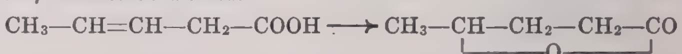
β-Hydroxybutyric acid — Crotonic acid

The γ-hydroxy and δ-hydroxy acids yield lactones.



γ-Hydroxybutyric acid — Butyrolactone

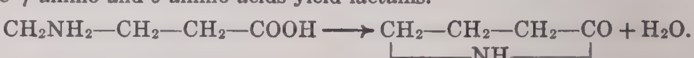
There are other methods for producing lactones, as, for example, by heating $\beta\gamma$ or $\gamma\delta$ unsaturated acids.



The amino acids yield analogous products. The α-amino acids, when heated, yield cyclic anhydrides (see p. 194). The β-amino acids lose ammonia, forming salts of unsaturated acids.

$$CH_3{-}CHNH_2{-}CH_2{-}COOH \longrightarrow CH_3{-}CH{=}CH{-}COONH_4.$$

The γ-amino and δ-amino acids yield lactams.



γ-Aminobutyric acid — Butyrolactam

Acid Chlorides

Chlorine is substituted for the hydroxyl in the carboxyl group when an acid is treated with phosphorus trichloride or pentachloride or when the salt of an acid is treated with phosphorus pentachloride or phosphorus oxychloride. The substitution product, $R \cdot CO \cdot Cl$, is known as an acid chloride. The corresponding bromides may be formed in the same way by using the phosphorus compounds of bromine. Iodides and

fluorides are known, but they are unimportant. Typical reactions are indicated by the following equations:

(1) $3CH_3COOH + PCl_3 \longrightarrow 3CH_3COCl + H_3PO_3$;

(2) $CH_3COONa + PCl_5 \longrightarrow CH_3COCl + NaCl + POCl_3$;

(3) $2CH_3COONa + POCl_3 \longrightarrow 2CH_3COCl + NaCl + NaPO_3$.

These equations do not represent quantitative reactions. It is obvious that part of the acid chloride will be formed according to equation (3) when PCl_5 acts on a salt, for $POCl_3$, one of the reaction products in (2), can also act upon the salt. Equation (1) fails to account for the hydrogen chloride which is formed in abundance when phosphorus trichloride acts upon acetic acid. Brooks * has proved that the hydrogen chloride is formed in secondary reactions between the acid chloride and acetic acid and between the acid chloride and phosphorous acid:

(4) $CH_3COOH + CH_3COCl \longrightarrow (CH_3CO)_2O + HCl$;

(5) $H_3PO_3 + CH_3COCl \longrightarrow P\begin{cases}(OH)_2 \\ OCOCH_3\end{cases} + HCl$.

The acid chlorides having fewer than sixteen carbon atoms are liquids. The lower members fume in moist air and boil at low temperatures. They all react with water, forming the corresponding organic acid and hydrochloric acid.

They react readily with alcohols, amines, alkyl magnesium halides, ammonia, salts of organic acids, and other reagents. They are useful, therefore, as sources of esters, amides, ketones, and acid anhydrides.

Typical reactions of the acid chlorides are represented by the following equations:

(1) $CH_3 \cdot CO \cdot Cl + C_2H_5OH \longrightarrow CH_3 \cdot CO \cdot OC_2H_5 + HCl$.

(2) $CH_3 \cdot CO \cdot Cl + C_2H_5NH_2 \longrightarrow CH_3 \cdot CO \cdot NHC_2H_5 + HCl$.

(3) $CH_3 \cdot CO \cdot Cl + AgCN \longrightarrow CH_3 \cdot CO \cdot CN + AgCl$.

(4) $CH_3 \cdot CO \cdot Cl + 2C_2H_5MgCl$

$$\longrightarrow CH_3 \cdot C\begin{cases}C_2H_5 \\ OMgCl \\ C_2H_5\end{cases} + MgCl_2.$$

On hydrolysis, the product formed in equation (3) yields an α-ketonic acid,

$$CH_3 \cdot CO \cdot CN + 2H_2O \longrightarrow CH_3 \cdot CO \cdot COOH + NH_3,$$

* Benj. T. Brooks, *J. Am. Chem. Soc.*, **34**, 492 (1912).

and the compound formed in the reaction represented by equation (4) yields a tertiary alcohol.

$$CH_3 \cdot C\begin{array}{l} \diagup C_2H_5 \\ -OMgCl \\ \diagdown C_2H_5 \end{array} + H_2O \longrightarrow CH_3 \cdot C\begin{array}{l} \diagup C_2H_5 \\ -OH \\ \diagdown C_2H_5 \end{array} + MgClOH.$$

Some aryl magnesium halides combine with acid chlorides in such a way as to produce ketones instead of tertiary alcohols:*

$$R \cdot CO \cdot Cl + R'MgCl \longrightarrow R \cdot CO \cdot R' + MgCl_2.$$

Formyl chloride, $H \cdot COCl$, has not been isolated in a pure state. It decomposes into hydrogen chloride and carbon monoxide. In many cases, however, a mixture of HCl and CO responds to the tests one would expect to obtain with the chloride of formic acid, and this mixture is often called formyl chloride.

Phosgene, or carbonyl chloride, $COCl_2$ (a derivative of carbonic acid), is made by the direct addition of chlorine to carbon monoxide under the catalytic influence of light or charcoal. The liquid boils at 8°. It is extremely poisonous and has been used extensively in gas warfare. It is very soluble in benzene and in toluene. It fumes in moist air, forming carbon dioxide and hydrogen chloride, and is decomposed by alcohol with the formation of hydrogen chloride and chloroformic ester:

$$C{=}O\begin{array}{l} \diagup \boxed{Cl \quad H} OH \\ \\ \diagdown \boxed{Cl \quad H} OH \end{array} \longrightarrow CO_2 + H_2O + 2HCl;$$

$$C{=}O\begin{array}{l} \diagup Cl \\ \\ \diagdown \boxed{Cl \quad H} OC_2H_5 \end{array} \longrightarrow C{=}O\begin{array}{l} \diagup Cl \\ \\ \diagdown OC_2H_5 \end{array} + HCl.$$

Urethane, a valuable hypnotic, is prepared from chloroformic ester by treatment with ammonia:

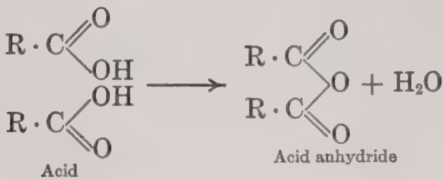
$$C{=}O\begin{array}{l} \diagup Cl \\ \\ \diagdown OC_2H_5 \end{array} + 2NH_3 \longrightarrow C{=}O\begin{array}{l} \diagup NH_2 \\ \\ \diagdown OC_2H_5 \end{array} + NH_4Cl.$$

Urethane is a colorless crystalline body (m.p. 50°, b.p. 180°) having a faint odor. Many other esters of carbamic acid have similar physiological properties and are used as sedatives.

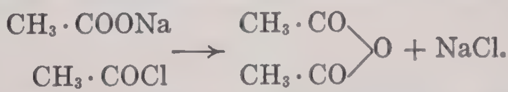
* Acree, *Ber.*, **37**, 625, 2753 (1904).

Acid Anhydrides

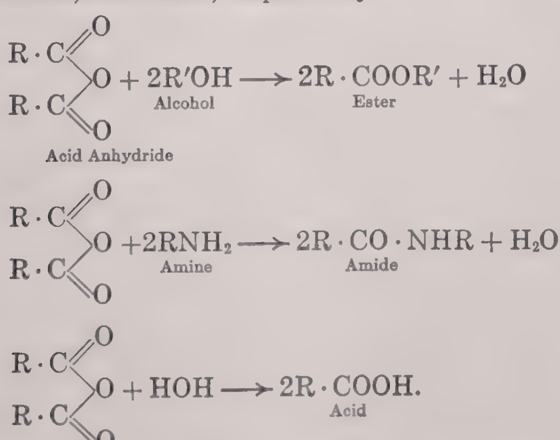
The removal of one molecule of water from two molecules of a monobasic acid results in the formation of an acid anhydride.



In some cases the dehydration may be accomplished by warming the acid with phosphorus pentoxide; but the result is usually achieved by other means. An acid anhydride may be made by distilling a mixture of an acid chloride and a salt of the acid. Acetic anhydride is easily prepared by this method.



Properties. The anhydrides of low molecular weight are colorless liquids, the higher members are solids. They are less reactive than the acid chlorides. Still they combine with alcohols, amines, and water, as do the acid chlorides, yielding esters, amides, and acids, respectively.



With metallic oxides and hydroxides the anhydrides act like the free acids in forming salts. The lower members are more

reactive than those of high molecular weight. A few of the solid anhydrides may be crystallized from water without reverting to the hydrated form.

The true anhydride of formic acid, $(HCO)_2O$, has never been prepared. When treated with a dehydrating agent, a molecule of water is eliminated from one molecule of formic acid and carbon monoxide is formed. Carbon monoxide can hardly be regarded as a true anhydride of the acid, for it does not dissolve in water with the regeneration of the acid. The gas does dissolve, however, in molten metallic hydroxides, forming salts of formic acid.

Acid			Acid Chloride		Anhydride		Amide	
	B.P.	Sp. Gr.	B.P.	Sp. Gr.	B.P.	Sp. Gr.	B.P.	M.P.
Acetic	118°	1.050(20°)	51°	1.105(20°)	136.5°	1.078(21°)	222°	82°
Propionic	141°	1.017(0°)	80°	1.065(20°)	168.6°	1.034(0°)	213°	79°
Butyric (*n*)	162°	0.975(0°)	101°	1.028(20°)	192°	0.978(15°)	216°	115°
Butyric (*iso*)	154°	0.965(0°)	92°	1.018(20°)	182°	0.958(16°)	220°	129°
Valeric (*n*)	185°	0.956(0°)	128°	1.016(15°)				116°
Valeric (*iso*)	174°	0.947(0°)	115°	0.989(20°)	215°	0.929(27°)	232°	129°
Trimethyl acetic	15°	0.905(50°)	106°		190°			155°
Caproic (*n*)	205°	0.945(0°)	152°		243°	0.928(17°)	255°	98°
Heptylic (*n*)	223°	0.921(15°)	175°	0.959(20°)	258°	0.912(17°)	258°	95°
Caprylic (*n*)	237.5°	0.910(20°)	198°	0.973(8°)	285°			98°
Palmitic (*n*)	272° *	0.853(62°)	192° †					105°
Stearic (*n*)	291° *	0.845(69°)	215° †					109°

* At 100 m.m. † 15 m.m.

ESTERS

Alcohols and acids combine with the elimination of water and the formation of compounds known as esters. The reaction between acetic acid and ethyl alcohol is typical:

$$CH_3 \cdot COOH + C_2H_5OH \longrightarrow CH_3COOC_2H_5 + H_2O.$$

The equation reminds one of the neutralization of an acid by a base. The resemblance, however, is only formal. Alcohol is not a base and the reaction indicated above is not ionic. There is some evidence that in the formation of water between the two reagents the hydroxyl comes from the acid and the hydrogen from the alcohol. A mixture of hydrochloric and acetic acids, for example, acts upon alcohol to form ethyl acetate and practically no ethyl chloride, although if the reaction were between alcoholic hydroxyl and hydrogen ions the formation of the chloride would be favored by the extensive ionization of the hydrochloric acid. In forming the ester, ethyl chloride, C_2H_5Cl, the hydrogen necessarily comes from the acid and the hydroxyl from the alcohol; but in forming ethyl acetate the hydrogen may be furnished by the alcohol and the hydroxyl by the acid or vice versa. The fact that in the mixture the reaction with acetic acid predominates, notwithstanding its weaker character, supports the opinion that the ordinary ions of the acid are not involved in ester formation. An analogous reaction with mercaptans throws some light on the question. Two possible courses for the action of acids and mercaptans are represented in the equations:

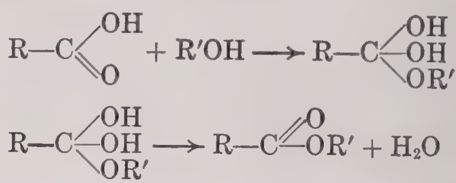
$$(1)\ R \cdot CO \boxed{OH + H} SR \longrightarrow RCOSR + H_2O;$$

$$(2)\ R \cdot COO \boxed{H + HS} R \longrightarrow RCOOR + H_2S.$$

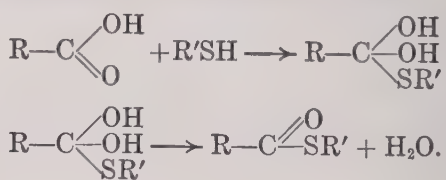
The reaction actually proceeds according to the first equation, splitting off water rather than hydrogen sulphide, and indicating that in the formation of thioesters the hydroxyl group is removed from the acid.*

* Pratt and Reid, *J. Am. Chem. Soc.*, **37**, 1934 (1915). Reid, *Am. Chem. J.*, **43**, 489 (1910).

Probably an addition product is first formed between the alcohol or mercaptan and the acid. Subsequent elemination of water from the unstable intermediate product would form the ordinary ester in one case and the thioester in the other. With alcohol we have



and with a mercaptan the mechanism is similar



There is no direct proof that these equations accurately represent the actual mechanism of ester formation. The intermediate product, having two hydroxyl groups on the same carbon atom, has never been isolated.

Esters occur in great abundance in nature. All of the vegetable and animal fats and oils belong to this class of compounds, and many of the flavors and perfumes of fruits and flowers are due to esters. Artificial perfumes and synthetic flavors are prepared in commercial laboratories from the lower acids and alcohols; thus, methyl alcohol and butyric acid yield an ester methyl butyrate, $C_3H_7 \cdot COOCH_3$, which is on the market as a substitute for the flavor of pineapple. Isoamyl acetate, $CH_3 \cdot COOC_5H_{11}$, is known as pear oil, and octyl acetate, $CH_3 \cdot COOC_8H_{17}$, has the odor and flavor of oranges.

Esters may be hydrolyzed by boiling with dilute acids or alkalies, or by prolonged heating with steam, the original acid and alcohol being regenerated. Isomeric esters are easily distinguished from each other by their hydrolysis products. Thus, ethyl acetate, $CH_3COOC_2H_5$, takes up one molecule of water and forms acetic acid, $CH_3 \cdot COOH$, and ethyl alcohol, C_2H_5OH; whereas the isomeric ester, methyl propionate, $C_2H_5COOCH_3$, when hydrolyzed, yields propionic acid and methyl alcohol.

Ethyl acetate. Ethyl acetate, $CH_3 \cdot COOC_2H_5$ (b.p. 77°, sp. gr. 0.9028), is formed by the action of ethyl alcohol on acetic acid. It is a clear, colorless liquid with a pleasant, fruity odor. It is slightly soluble in water (8.6 parts per 100) and miscible in all proportions with alcohol or ether. Since the reaction is reversible, it is not possible to convert the acid and alcohol quantitatively into the ester. Equilibrium is established when the rate of hydrolysis is equal to the rate of ester formation:

$$CH_3 \cdot COOH + C_2H_5OH \rightleftarrows CH_3 \cdot COOC_2H_5 + H_2O.$$

If equi-molal quantities of the acid and alcohol are used, equilibrium is reached when two thirds of the acid has been changed. The condition of equilibrium is almost independent of the temperature (65.2 per cent at 10°, 66.5 per cent at 220°), but the rate of approach to equilibrium is greatly increased by raising the temperature.

If, at the beginning of the reaction, we have a mols of acid and b mols of alcohol; and if, when equilibrium is established, x mols of acid and of alcohol have been used in forming x mols of ester and of water, then

$$\frac{x^2}{(a-x)(b-x)} = k.$$

The numerical value of the equilibrium constant, k, may be calculated by substituting in this equation the values indicated in the last paragraph:

$$\frac{(\frac{2}{3})(\frac{2}{3})}{(\frac{1}{3})(\frac{1}{3})} = k, \text{ or } k = 4.$$

With k known, the quantity of ester that will be formed in any mixture of pure alcohol and acid may be calculated. Thus, if we begin with 1 mol of acetic acid and 2.9 mols of alcohol, equilibrium will be reached when $\frac{x^2}{(1-x)(2.9-x)} = 4$. The conversion of acid to ester in this case amounts to nine tenths of the theoretical value. In actual practice the relative costs of materials determine the excess of the cheapest reagent that can be employed economically to increase the percentage yield on the basis of the more expensive reagent. Another practical means of favoring the reaction in either direction is that of withdrawing one of the products from the field of action. The activity of the water formed in esterification is reduced by the presence of sulphuric acid. If sulphuric acid is added, the active mass of water formed is kept very low, the value given for k can hardly be attained, and the reaction goes almost to completion. The equation given above cannot be applied when a dehydrating agent is present, for the effect of such an agent in reducing the activity of the water introduces a new factor.

The usual laboratory procedure for the preparation of ethyl acetate consists of mixing equal quantities of alcohol and concentrated sulphuric acid, heating to 140°, then adding a mixture of equal quantities of alcohol and glacial acetic acid. The alcohol and acid mixture is introduced by means of a dropping funnel at about the same rate that the ester distills over.

The mechanism of the reaction in the presence of sulphuric acid probably involves the formation of ethyl sulphuric acid, $C_2H_5HSO_4$, and a subsequent reaction between this compound and acetic acid in which the sulphuric acid is regenerated and ethyl acetate is formed.*

Fats

The fats and oils, so widely distributed in animal and vegetable tissues, are esters of the trihydric alcohol, glycerol. The principal acids combined with glycerol in the natural fats are stearic, $C_{17}H_{35}COOH$, palmitic, $C_{15}H_{31}COOH$, oleic, $C_{17}H_{33}COOH$, and butyric, C_3H_7COOH. One molecule of glycerol combines with three molecules of acid to form a fat. The three acid molecules may be alike or different. Stearin, palmitin, and olein are represented by the following structures:

$$\begin{array}{l} CH_2 \cdot O \cdot CO \cdot C_{17}H_{35} \\ | \\ CH \cdot O \cdot CO \cdot C_{17}H_{35} \\ | \\ CH_2 \cdot O \cdot CO \cdot C_{17}H_{35} \end{array} \qquad \begin{array}{l} CH_2 \cdot O \cdot CO \cdot C_{15}H_{31} \\ | \\ CH \cdot O \cdot CO \cdot C_{15}H_{31} \\ | \\ CH_2 \cdot O \cdot CO \cdot C_{15}H_{31} \end{array}$$

Tristearin Tripalmitin

$$\begin{array}{l} CH_2 \cdot O \cdot CO \cdot C_{17}H_{33} \\ | \\ CH \cdot O \cdot CO \cdot C_{17}H_{33} \\ | \\ CH_2 \cdot O \cdot CO \cdot C_{17}H_{33} \end{array}$$

Triolein

* Sulphuric acid acts upon alcohol in a variety of ways. The reaction products and the conditions under which they are formed have been investigated by Evans and Albertson. The following equations represent the principal reactions:

(1) $C_2H_5OH + H_2SO_4 \longrightarrow C_2H_5HSO_4 + H_2O$;

(2) $2C_2H_5OH + H_2SO_4 \longrightarrow C_2H_5OC_2H_5 + H_2SO_4 \cdot H_2O$;

(3) $C_2H_5OH + H_2SO_4 \longrightarrow C_2H_4 + H_2SO_4 \cdot H_2O$;

(4) $2C_2H_5OH + H_2SO_4 \longrightarrow (C_2H_5)_2SO_4 + H_2O$;

(5) $C_2H_5OH + H_2SO_4 \longrightarrow CH_2OH \cdot CH_2SO_2OH + H_2O$;

(6) $C_2H_5OH + 2H_2SO_4 \longrightarrow CH_2HSO_4 \cdot CH_2SO_2OH + H_2O$.

Evans and Albertson, *J. Am. Chem. Soc.*, **39**, 456 (1917).

The natural fats are mixtures of these esters with smaller quantities of glycerol esters of other acids and with mixed esters, that is, esters in which two or three different acids are in combination with the same glycerol residue.

Oleopalmitobutyrate occurs in butter fat. Human fat consists, primarily, of a mixture of tripalmatin and dioleostearin.

$$\begin{array}{l} CH_2 \cdot O \cdot CO \cdot C_{17}H_{33} \\ | \\ CH \cdot O \cdot CO \cdot C_{15}H_{31} \\ | \\ CH_2 \cdot O \cdot CO \cdot C_3H_7 \end{array} \qquad \begin{array}{l} CH_2 \cdot O \cdot CO \cdot C_{17}H_{33} \\ | \\ CH \cdot O \cdot CO \cdot C_{17}H_{33} \\ | \\ CH_2 \cdot O \cdot CO \cdot C_{17}H_{35} \end{array}$$

Oleopalmitobutyrate   Dioleostearin

Butter contains glycerol esters of stearic, palmitic, oleic, myristic, capric, caprylic, caproic, and butyric acids. About 90 per cent of butter fat consists of esters of the first three acids in the list. Tristearin is the chief component of beef tallow, and triolein predominates in cottonseed oil.

Olive oil contains from 25 per cent to 30 per cent of tripalmitin and about 65 per cent of triolein. Linseed oil contains many unsaturated fats, including esters of linoleic, linolenic, and isolinolenic acids. The last two acids are highly unsaturated. They have the formula $C_{17}H_{29} \cdot COOH$. The structures are unknown. Linoleic acid contains two double bonds and has the formula $C_{17}H_{31} \cdot COOH$. These unsaturated acids and the esters derived from them absorb oxygen from the air, forming saturated compounds. It is due to this property that linseed oil is a valuable component of varnishes and paints. It is called a drying oil. The oxidation product is a firm, smooth, solid substance. Linseed oil dries faster if it has been boiled with lead acetate or with litharge. These substances are practically insoluble in the oil, but enough is held in solution to catalyze the union of the oil with oxygen of the air. Linoleum is made from boiled linseed oil and ground cork.

The Iodine Value. Fats may often be identified or distinguished from each other by estimating the quantity of the unsaturated esters present. This is accomplished by measuring the iodine absorbed. Two atoms of iodine will be taken up at each double bond. A weighed quantity of fat is dissolved in chloroform and titrated with an alcoholic solution of iodine. The iodine number is the per cent of iodine absorbed, calculated on the basis of the weight of oil used; that is, $\frac{\text{wt. of iodine}}{\text{wt. of fat}} \times 100$. The iodine value of cottonseed oil is 111 to 116, and of cocoanut oil, 8.5 to 9.0.

The Reichert-Meissel Number. Fatty acids of low molecular weight are soluble in water and volatile with steam. Higher members either do not distill with steam or fail to dissolve in the distillate. The quantity of ester of low molecular weight may be estimated by saponifying the fat, acidifying with sulphuric acid, distilling with steam, and titrating the cold filtered distillate with an alkali. The Reichert-Meissel number is the number of cubic centimeters of tenth normal base required to neutralize the water-soluble volatile acid found in five grams of fat. The Reichert-Meissel number of butter is 22–30, of oleomargarine, 0.5–1.5, and of lard, 0.3–0.6.

Fats may be hydrolyzed by boiling with dilute acids or alkalies or by heating with steam. The products formed are glycerol and the free fatty acids or, if boiled with alkalies, glycerol and the salts of fatty acids (soaps). Hydrolysis by an alkali is referred to as saponification.

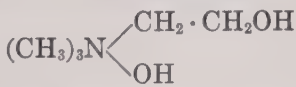
$$\begin{array}{lcl} CH_2 \cdot O \cdot CO \cdot C_{17}H_{35} & & CH_2OH \\ | & & | \\ CH \cdot O \cdot CO \cdot C_{17}H_{35} + 3NaOH & \longrightarrow & CHOH + 3C_{17}H_{35}COONa \\ | & & | \\ CH_2 \cdot O \cdot CO \cdot C_{17}H_{35} & & CH_2OH \end{array}$$

Since all natural sources of fats yield mixed esters, the soaps ordinarily manufactured are not pure salts. They are mixtures of the salts of several acids — chiefly stearic, palmitic, and oleic — in which more or less water, glycerol, and alkali are incorporated. Different soaps are made by varying the relative proportions of different fats, by using different bases, by incorporating different amounts of glycerol, and so on. Hard soaps and soap powders are made by saponifying fats with sodium hydroxide. Soft soaps are potassium salts. Calcium, magnesium, and barium salts of the fatty acids are not soluble in water. When a soluble soap is added to " hard " water, a flocculent precipitate of the calcium or magnesium soap separates, and the water is " softened " as effectively as if accomplished by precipitating these metals as hydroxides by the addition of sodium hydroxide or ammonia. The use of soap for softening water is not an economical practice.

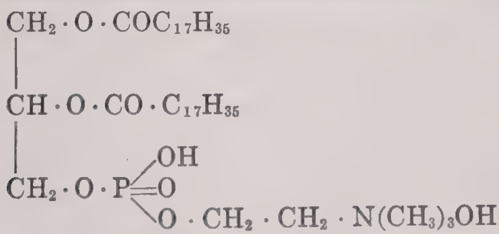
The free fatty acids are prepared in large quantities by hydrolyzing the fats with superheated steam. Stearic acid freed by pressure from the softer acids is mixed with a little paraffin to render it less brittle and used in the manufacture of candles. The oleic, palmitic, and stearic acids pressed out of the mixture are used in the manufacture of soaps.

Lecithins

Lecithins, though less abundant than fats, occur in almost every cell of the animal organism. They are like the fats in many respects. When boiled with dilute acids, lecithins take up water, forming free fatty acids, choline, and glycerophosphoric acid. The latter is also partly hydrolyzed to phosphoric acid and glycerine, so that the ultimate hydrolysis products are the same as for the fats plus phosphoric acid and choline. Choline,



belongs to the class of compounds known as ptomaines. In lecithins choline is combined with phosphoric acid, forming a group which takes the place of one acid radical in the fats. The formula of distearyl-lecithin, a typical member of the group, is:



Lecithins and other lipoids (fatlike bodies) are especially abundant in nervous tissue, but they are not confined to any particular kind of tissue nor to the animal organism. They are present in small quantities in plants.

Lecithins dissolve in alcohol, chloroform, ether, benzene, and carbon bisulphide. They are insoluble in water, and only slightly soluble in acetone. Most of them crystallize from alcohol in thin, transparent plates, colorless, or slightly yellow. A preparation of a lecithin can be made by grinding the brain of an animal with a little sand and allowing it to stand under cold ether two or three days. Acetone is then added to the clear ether extract and lecithin is precipitated.

Esters of Inorganic Acids

Nitrous esters. Sodium nitrite acts upon a mixture of alcohol and sulphuric acid to form the nitrous acid ester of the alcohol:

$$C_2H_5OH + HONO \longrightarrow C_2H_5ONO + H_2O.$$

The same product may be formed from alcohol and nitrosyl chloride:

$$C_2H_5OH + ClNO \longrightarrow C_2H_5ONO + HCl.$$

Silver nitrite acts upon many alkyl halides, precipitating a silver halide and forming two different alkyl derivatives of nitrous acid having the same empirical formula. One of these isomers is an ester, the other a nitro-body. The nitrogen is attached directly to carbon in the latter and to oxygen only in the ester:

$$C_2H_5I + AgNO_2 \longrightarrow \underset{\text{Nitroethane}}{C_2H_5{-}N\genfrac{}{}{0pt}{}{\nearrow O}{\searrow O}} + AgI;$$

$$O$$

$$C_2H_5I + AgNO_2 \longrightarrow \underset{\text{Ethyl nitrite}}{C_2H_5{-}O{-}N{=}O} + AgI.$$

The ester, ethyl nitrite, is readily reduced to ethyl alcohol, C_2H_5OH, and hydroxylamine, NH_2OH, or to alcohol, water, and ammonia. Nitroethane, under the same treatment, is reduced to ethyl amine, $C_2H_5NH_2$, and water. These reactions indicate that the alkyl radical is attached to oxygen in one compound and to nitrogen in the other. Nitrogen attached to carbon is not removed in reduction processes at ordinary temperatures.

Nitrous esters are so easily hydrolyzed that they may be used as sources of free nitrous acid in many reactions. From hydrazine, in alkaline aqueous solution with ethyl nitrite, hydrazoic acid is formed:

$$C_2H_5ONO + H_2O \longrightarrow C_2H_5OH + HONO;$$

$$HONO + NH_2{-}NH_2 \longrightarrow 2H_2O + HN_3.$$

These esters are used as sources of nitrous acid in the diazo reactions also.

Silver nitrite acts upon methyl iodide to form nitro methane, CH_3NO_2, free from the isomeric ester; but the higher alkyl halides yield mixed products.

Nitric esters. Esters of nitric acid are formed by the direct action of concentrated nitric acid on alcohols at 0° to 5° C. At higher temperatures the acid acts as an oxidizing agent. Nitric esters are combustible, and if heated under pressures greater than one atmosphere, they may explode. They boil

at temperatures higher than the boiling points of the corresponding nitrites.

Alkyl Radical R	Nitrate $R \cdot O \cdot NO_2$	Nitrite $R \cdot O \cdot NO$	Nitro Compound $R \cdot NO_2$
Methyl	66°	-12°	101°
Ethyl	87°	17°	113°
n-Propyl	110°	57°	131°
iso-Propyl	102°	39°	119°
n-Butyl	136°	75°	151°
iso-Butyl	123°	67°	140°

Nitroglycerine. The most important ester of nitric acid is glyceryl trinitrate. Though commonly called nitroglycerine it is not a true nitro-body for the NO_2 group is not attached to carbon. It is formed by injecting a spray of glycerol into a mixture of concentrated nitric and sulphuric acids which is agitated by compressed air.

$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + 3HNO_3 \longrightarrow \begin{array}{l} CH_2ONO_2 \\ | \\ CHONO_2 \\ | \\ CH_2ONO_2 \end{array} + 3H_2O.$$

The temperature of the mixture is held between 20° and 30° C. and the time required for nitration is about one hour. The nitroglycerine floats on the waste acids. It is drawn off and washed with water and with dilute sodium carbonate solutions until free from acids.

Nitroglycerine (m.p. 8°, sp. gr. 1.60) is a sweet, poisonous, oily liquid, colorless and odorless when pure but pale yellow as ordinarily prepared. It is practically insoluble in water; soluble in alcohol, benzene, and chloroform. It explodes when struck with a hammer or subjected to any other sudden shock. It is usually detonated by means of a mercury fulminate cap. The products of the explosion are carbon dioxide, water, nitrogen, oxygen, and nitrogen oxides. The energy released is equivalent to about six kilogrammeters per gram. When exploded in its own volume, the pressure developed is about 160 tons per square inch.

Dynamite is made by absorbing nitroglycerine in wood pulp or in infusorial earth. In this form the substance may be transported safely. Sodium nitrate, potassium nitrate, and

sulphur are components of some brands of dynamite and blasting powders.

Blasting gelatines are made by absorbing nitroglycerine in nitrocellulose or in mixtures of nitrocellulose, wood pulp, and inorganic nitrates or chlorates. These are among the most powerful explosives known.

Sulphuric esters. Ethyl hydrogen sulphate, $C_2H_5HSO_4$, is an oily liquid (sp. gr. 1.316) which decomposes before boiling. It is formed from alcohol and concentrated sulphuric acid at 100° C. or from ethylene gas and fuming sulphuric acid. Its barium salt is soluble in water, a property that makes possible its separation from the unchanged acid. When heated with water, it regenerates the alcohol and acid. If heated with alcohol, it produces sulphuric acid and ether. Alkyl halides and cyanides and many other types of compounds may be prepared by means of this reactive ester:

$$C_2H_5HSO_4 + HOH \longrightarrow C_2H_5OH + H_2SO_4;$$
$$C_2H_5HSO_4 + C_2H_5OH \longrightarrow C_2H_5 \cdot O \cdot C_2H_5 + H_2SO_4;$$
$$C_2H_5HSO_4 + HBr \longrightarrow C_2H_5Br + H_2SO_4;$$
$$C_2H_5HSO_4 + KCN \longrightarrow C_2H_5 \cdot CN + KHSO_4;$$
$$C_2H_5HSO_4 + \text{heat} \longrightarrow C_2H_4 + H_2SO_4.$$

Methyl sulphate, $(CH_3)_2SO_4$ (b.p. 188°, m.p. −10°, sp. gr. 1.35), is frequently employed to introduce the methyl group into alcohols and amines. The hydrogen atoms in the groups OH, NH_2, and NH are replaced by methyl groups when treated with this ester. Sulphur trioxide acts on methyl alcohol at −5° to 0°, producing methyl hydrogen sulphate. This product when distilled under reduced pressure yields the neutral ester:

$$2CH_3HSO_4 \longrightarrow (CH_3)_2SO_4 + H_2SO_4.$$

Halogen acids. The esters of hydrochloric, hydrobromic, and hydroidic acids have been discussed as alkyl halides.

ACID AMIDES

The acid amides are formed by replacing hydrogen of ammonia by acyl radicals. They are primary, secondary, or tertiary, depending upon the number of hydrogen atoms replaced.

$R \cdot CONH_2$,	$(R \cdot CO)_2NH$,	$(R \cdot CO)_3N$.
Primary amide	Secondary amide	Tertiary amide

The secondary and tertiary compounds are of little importance and quaternary amides are unknown. With the exception of formamide, a liquid, the primary compounds are colorless solids, soluble in water, and, when pure, they are odorless. The lower members can be distilled under atmospheric pressure without decomposition. They may be prepared from many acid derivatives:

1. By the action of ammonia on an acid chloride,

$$CH_3 \cdot COCl + HNH_2 \longrightarrow HCl + CH_3 \cdot CONH_2.$$

2. By the action of ammonia on an ester,

$$CH_3 \cdot CO\cancel{O}C_2H_5 + HNH_2 \longrightarrow C_2H_5OH + CH_3 \cdot CONH_2.$$

The formation of acetamide, as indicated in the last equation, is accomplished by mixing the ester with twice its volume of a concentrated solution of ammonia, and allowing the mixture to stand a few hours. The amide is isolated from the mixture by evaporating the water, alcohol, and excess of ammonia. Finally, the acetamide distills (at 222°) and condenses to a colorless crystalline product which melts at 82°.

3. By heating the ammonium salt of an acid in a sealed tube at 230° for five or six hours,

$$CH_3 \cdot COONH_4 \longrightarrow H_2O + CH_3 \cdot CONH_2.$$

4. By the union of water with alkyl cyanides,

$$CH_3 \cdot CN + H_2O \longrightarrow CH_3 \cdot CONH_2.$$

The addition is accomplished through the agency of hydrogen peroxide in alkaline solution. The reverse of this reaction occurs when an amide is heated with a dehydrating agent.

Methyl cyanide is obtained when acetamide is distilled in the presence of phosphorus pentoxide:

$$CH_3 \cdot CONH_2 \longrightarrow CH_3 \cdot CN + H_2O.$$

Properties. The amides are readily hydrolyzed by heating with water, the hydrolysis being catalyzed by hydrogen ions, and to a greater extent by hydroxide ions:

$$CH_3 \cdot CONH_2 + HOH \longrightarrow CH_3 \cdot COOH + NH_3.$$

They differ in this respect from the amines. Nitrogen attached to carbon in a positive group is not removed by hydrolysis.

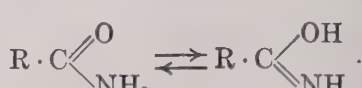
Amides are converted into amines through the agency of bromine and potassium hydroxide:

$$CH_3CONH_2 + Br_2 + 4KOH$$
$$\longrightarrow CH_3NH_2 + K_2CO_3 + 2KBr + 2H_2O.$$

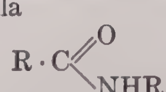
The mechanism of this reaction is discussed under the Beckmann rearrangement.

Tautomerism. When two or more isomers pass rapidly from one form to another, under the influence of changing environment, they are called tautomers; and the phenomenon is known as tautomerism. The amides display this property to some extent. The purines (p. 190) and the proteins (p. 210) are characterized by the amide group, —CO—NH—, and these compounds also exist in tautomeric forms. The structure of the group referred to above may be —CO—NH— (*keto* form) or —COH=N— (*enol* form).

The amides, though neutral to litmus, form salts with strong acids, thus exhibiting, in aqueous solution, a weak basic property. They also form salts with strong bases. On account of the amphoteric character of the amides it is assumed that they exist in two forms which, in solution, are in tautomeric equilibrium:



Tautomerism in the case of free amides has not been fully established, but alkyl derivatives of both forms actually exist. Those having the formula



are called normal alkyl amides and those of the type

$$R \cdot C \begin{array}{l} \diagup OR \\ \diagdown\!\!\diagdown NH \end{array}$$

are known as imino-ethers.

A classical example of tautomerism is discussed under Aceto-acetic Ester (p. 386). It was a study of the properties of this compound that led to the development of the theory of tautomerism. For methods of estimating the composition of an equilibrium mixture of keto and enol forms see Paul Grossmann, *Zeit. physik. Chem.*, 109, 305 (1924). Another example is found in the oximes which appear to have the formulas

$$R_2C{=}N{-}OH \quad \text{and} \quad R_2C \begin{array}{l} \diagup O \\ \quad | \\ \diagdown NH \end{array}$$

They are derived from aldehydes or ketones through the action of hydroxylamine, H_2NOH. But water may be eliminated between hydroxylamine and a carbonyl group in two ways. With acetone, for example, the following reactions are possible:

$$\begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C:O + \begin{array}{l} H \diagdown \\ H \diagup \end{array} N \cdot OH \longrightarrow \underset{\text{I}}{\begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C:N \cdot OH} + H_2O;$$

$$\begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C:O + \begin{array}{l} HO \diagdown \\ H \diagup \end{array} N \cdot H \longrightarrow \underset{\text{II}}{\begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C \begin{array}{l} \diagup O \\ \quad | \\ \diagdown N \cdot H \end{array}} + H_2O.$$

Which formula should be used to represent acetoxime? We might undertake to settle the question by making some derivative of the oxime and determining its structure. Acetoxime reacts with methyl iodide in neutral or slightly acid solution, giving methyl acetoxime, and in this compound the methyl group is attached to nitrogen, for reducing agents decompose it with the production of methyl amine and acetone.

Formula II accounts for this reaction and formula I fails:

$$\begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C \begin{array}{l} \diagup O \\ \quad | \\ \diagdown NH \end{array} + CH_3I \longrightarrow \begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C \begin{array}{l} \diagup O \\ \quad | \\ \diagdown NCH_3 \end{array} + HI,$$

$$\begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C \begin{array}{l} \diagup O \\ \quad | \\ \diagdown NCH_3 \end{array} + 2\,H \longrightarrow \begin{array}{l} CH_3 \diagdown \\ CH_3 \diagup \end{array} C{=}O + CH_3NH_2.$$

On the other hand, if we carry out the same reaction in alkaline solution, so that a salt of the oxime is first formed, the product obtained is isomeric with the one formed in acid solution. It does not yield methyl amine on reduction, and it is hydrolyzed by hydrochloric acid into acetone and methyl hydroxylamine, $H_2N \cdot OCH_3$, in which the methyl group is attached to oxygen. Formula I satisfies the requirements for this reaction and formula II fails:

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:NOH + NaOCH_3 \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:NONa + CH_3OH,$$

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:NONa + CH_3I \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:NOCH_3 + NaI,$$

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:NOCH_3 + H_2O \longrightarrow \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CO + H_2NOCH_3.$$

The environment determines which of the two formulas represents the compound. In acid solution acetoxime seems to have the structure represented by (II), but changes to (I) when it forms a salt in alkaline solution. Both forms are present in any neutral solution containing the free oxime. They are in tautomeric equilibrium and the transformation is rapid:

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:NOH \rightleftarrows \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C\!\!<\!\begin{matrix} O \\ | \\ NH \end{matrix}.$$

If we add to the solution a reagent that removes one of them, the equilibrium is disturbed and the other form goes rapidly into the structure required by the reagent present. Hence, in the presence of any reagent that acts selectively upon one of the structures, the oxime reacts as if it existed in the selected form only. It is possible, therefore, to isolate a derivative of either structure; but to get a pure specimen of the tautomeric compound itself is a difficult task and in many cases impossible. The two modifications of aceto-acetic ester and of some oximes and a few other tautomeric forms have been separated and each form isolated in a pure state; but the tautomeric amides have not been separated. As a matter of fact the term "tau-

tomerism" applies only to isomers of the type that cannot be readily separated. If the change in structure were not rapid and reversible, the different forms would not be tautomeric; they would be classified as ordinary structural isomers.

AMIDES OF DIBASIC ACIDS

One or both of the hydroxyls in a dibasic acid may be replaced by the amino group in the formation of amides. If the amide retains a free (unchanged) carboxyl, the compound is called an -amic acid. If both hydroxyls have been replaced, the compound is a neutral amide:

$$\underset{\text{Oxalic acid}}{\begin{array}{c} COOH \\ | \\ COOH \end{array}} \qquad \underset{\text{Oxamic acid}}{\begin{array}{c} CONH_2 \\ | \\ COOH \end{array}} \qquad \underset{\text{Oxamide}}{\begin{array}{c} CONH_2 \\ | \\ CONH_2. \end{array}}$$

Oxamide is a white, crystalline substance which is sparingly soluble in water. At 180° it sublimes with partial decomposition. Cyanogen and water are the principal decomposition products:

$$\begin{array}{c} CONH_2 \\ | \\ CONH_2 \end{array} \longrightarrow \begin{array}{c} CN \\ | \\ CN \end{array} + 2H_2O.$$

The diamides are formed by reactions analogous to those given for amides of monobasic acids. Ammonium oxalate, for instance, when heated with a dehydrating agent yields oxamide; and acid ammonium oxalate under similar treatment yields the white crystalline oxamic acid.

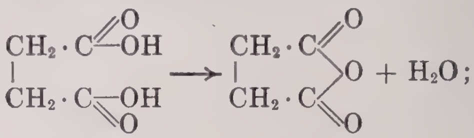
$$\begin{array}{c} COOH \\ | \\ COONH_4 \end{array} \longrightarrow \begin{array}{c} COOH \\ | \\ CONH_2 \end{array} + H_2O.$$

Succinic acid yields a monoamide, succinamic acid (I), and two diamides (II) and (III):

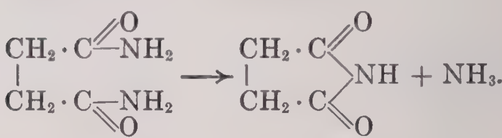
$$\underset{\text{I}}{\begin{array}{l} CH_2{-}CONH_2 \\ | \\ CH_2{-}COOH \end{array}} \qquad \underset{\text{II}}{\begin{array}{l} CH_2{-}CONH_2 \\ | \\ CH_2{-}CONH_2 \end{array}} \qquad \underset{\text{III}}{\begin{array}{l} CH_2{-}C(NH_2)_2 \\ | \qquad\quad \rangle O \\ CH_2{-}C:O \end{array}}$$

One of these diamides, when heated, yields ammonia, and a ring compound, succinimide. It is represented, therefore, by formula

II, the loss of ammonia corresponding to the loss of water when the free acid is converted into an anhydride:

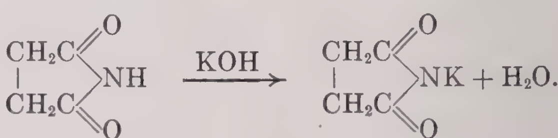


Succinic acid Succinic anhydride



Succinamide Succinimide

Succinimide (m.p. 126°, b.p. 288°) crystallizes with one molecule of water. It is neutral to litmus, but reacts with alcoholic potash, forming a salt:

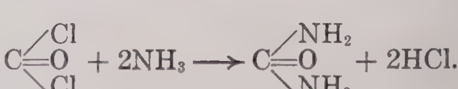


UREA

The diamide of carbonic acid, urea, is a compound of some importance. It was the first organic compound to be prepared by an artificial method. The synthesis was accomplished through the reversible conversion of ammonium cyanate into urea, a reaction first observed by Wohler (1828). The change occurs during the evaporation of an aqueous solution of ammonium cyanate:

$$NH_4CNO \rightleftharpoons CO(NH_2)_2.$$

Urea may be prepared by the action of ammonia on phosgene gas:



It crystallizes in colorless prisms, melting at 132°, and dissolves readily in water and in alcohol.

Urea constitutes from two to five per cent of the urine. The average amount excreted daily by an adult person is between

twenty-five and thirty-five grams. It is formed along with smaller quantities of uric acid, creatine, ammonia, and other nitrogen compounds as an oxidation product of the proteins in the living tissues. It may be obtained from urine by evaporation and extraction of the residue with hot alcohol, or in a more pure state by concentrating the sample through partial evaporation and acidifying with nitric acid. The slightly soluble urea nitrate, $CO(NH_2)_2HNO_3$, precipitates. The salt is decomposed by barium carbonate and the urea is separated from the resulting barium nitrate by extraction with alcohol. Oxalic acid also forms an insoluble salt of urea.

When heated above its melting point, urea decomposes with the liberation of ammonia and the production of cyanuric acid and biuret.

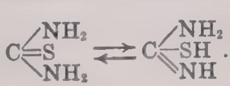
An alkaline solution of biuret ($NH_2 \cdot CO \cdot NH \cdot CO \cdot NH_2$) acquires a violet color when a solution of a copper salt is added. This is known as the biuret test and is mentioned in connection with the color reactions of the proteins.

The quantitative estimation of urea is accomplished by measuring the nitrogen evolved from a weighed sample when treated with an alkaline solution of sodium hypobromite:

$$CO(NH_2)_2 + 3NaOBr \longrightarrow 3NaBr + N_2 + CO_2 + 2H_2O.$$

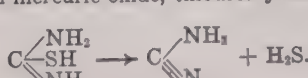
This reaction was used for many years as a basis for the clinical estimation of urea in urine. It is, however, entirely untrustworthy in this connection, for other nitrogen compounds found in urine respond to the test, and under pathological conditions some of these, such as ammonia, taurine, and amino acids, are present in considerable quantities.

Thiourea, the diamide of thiocarbonic acid, exists in two forms, which, in solution, establish a tautomeric equilibrium:

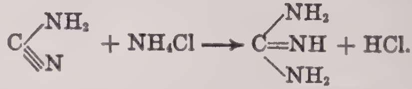


The free amide in the solid state is known only as colorless crystals (m.p. 172°), soluble in water and insoluble in alcohol. But many of its derivatives have been isolated in isomeric forms.

When warmed with mercuric oxide, thiourea yields cyanamide:

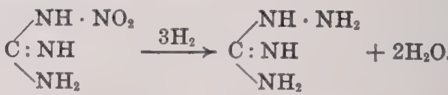


Guanidine, a colorless, crystalline, basic compound, is closely related to urea and thiourea. It may be prepared from cyanamide and an ammonium salt:



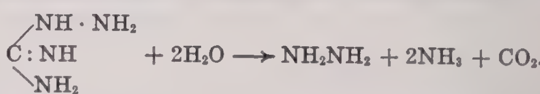
Guanidine

The hydrochloric acid is not liberated, but combines with the guanidine to form a salt. With concentrated nitric acid guanidine forms a nitro-compound and like any other nitro-body this compound can be reduced to an amine of corresponding structure:

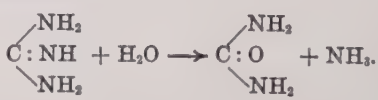


Nitroguanidine Aminoguanidine

Aminoguanidine undergoes hydrolysis in either acid or alkaline solution, the products being hydrazine, ammonia, and carbon dioxide:



Guanidine is also readily hydrolyzed in alkaline solution, the products being urea and ammonia:



POLYBASIC ACIDS

$C \genfrac{}{}{0pt}{}{=O}{-OH}$

Acids having two or more carboxyl groups in the molecule are produced by reactions analogous to those used for the synthesis of monobasic acids. The hydrolysis of compounds having more than one cyanide radical, the oxidation of alcohols having more than one $—CH_2OH$ group, or the oxidation of dialdehydes, are methods of general application. The important members of this series are the dibasic acids derived from normal (straight chain) hydrocarbons with the two carboxyl groups attached to the terminal carbon atoms.

They are colorless, crystalline solids. The compounds having an uneven number of carbon atoms are more soluble in water and melt at lower temperatures than those having approximately the same molecular weights but containing an even number of carbon atoms.

Name	Formula	Melting Point	Solubility in 100 g. Water, 20°
Oxalic	$COOH—COOH$	189.5°	8.6
Malonic	$COOH—CH_2—COOH$	133°	73.5
Succinic	$COOH—(CH_2)_2—COOH$	183°	5.8
Glutaric	$COOH—(CH_2)_3—COOH$	97.5°	63.9
Adipic	$COOH—(CH_2)_4—COOH$	153°	1.5
Pimelic	$COOH—(CH_2)_5—COOH$	105.5°	5
Suberic	$COOH—(CH_2)_6—COOH$	140°	0.16
Azelaic	$COOH—(CH_2)_7—COOH$	108°	0.24
Sebacic	$COOH—(CH_2)_8—COOH$	135°	0.10

OXALIC ACID

Oxalic acid, $C_2H_2O_4 \cdot 2H_2O$, is widely distributed in nature. In the form of its salts it occurs in many plants, especially in the oxalis family. Rhubarb contains a sufficient quantity to arrest the growth of organisms that cause decay, and the plant can be preserved for weeks by immersion in water without artificial sterilization. The acid is used in the manufacture of some dyes, and as a mordant in calico printing. It is the chief source of formic acid.

Oxalic acid crystallizes with two molecules of water, and in this form it is weighed for standardizing permanganate solutions for use in volumetric analysis. The reaction in acid solution is represented as follows:

$$5(COOH)_2 + 2MnO_4^- + 6H^+ \longrightarrow 2Mn^{++} + 10CO_2 + 8H_2O.$$

The hydrated acid loses water and sublimes, at 150°, with partial decomposition. When heated with concentrated sulphuric acid, it decomposes in the same way, yielding carbon dioxide, carbon monoxide and water, or carbon dioxide and formic acid:

$$\begin{array}{l} COOH \\ | \\ COOH \end{array} \longrightarrow CO_2 + CO + H_2O.$$

Oxalic acid is stable in the presence of some oxidizing agents; for example, concentrated nitric acid. It is made, commercially, by oxidizing starch or cellulose with concentrated nitric acid or by heating sawdust to 250° with a concentrated solution of sodium hydroxide.

It can be synthesized by the hydrolysis of cyanogen:

$$\begin{array}{l} CN \\ | \\ CN \end{array} + 4H_2O \longrightarrow \begin{array}{l} COONH_4 \\ | \\ COONH_4 \end{array}$$

or by rapidly heating sodium formate:

$$\begin{array}{l} HCOONa \\ \\ HCOONa \end{array} \longrightarrow \begin{array}{l} COONa \\ | \\ COONa \end{array} + H_2.$$

The last reaction is especially interesting, for it reveals a genetic relationship between oxalic and formic acids, the first members of the two most important series of the saturated acids. The preparation of formic acid from oxalic has been mentioned (p. 99).

MALONIC ACID

Malonic acid, $COOH—CH_2—COOH$, is a compound of prime importance on account of the many syntheses that can be made with the aid of its derivatives. The most useful derivative, malonic ester, and its reactions will be considered later.

Malonic acid is derived from acetic acid by a series of reactions that establish the constitution of the molecule. Chlorine acts upon acetic acid, producing a white crystalline derivative, chloracetic acid, having the formula $ClCH_2COOH$. Potassium cyanide reacts with chloracetic acid, as it does with alkyl halides, forming potassium chloride and leaving the cyanide radical attached to carbon. Cyanacetic acid, therefore, has the structure $CN \cdot CH_2 \cdot COOH$. The cyanide radical is always susceptible to hydrolysis, being thereby converted into the carboxyl group. Malonic acid is produced from cyanacetic by boiling it with dilute hydrochloric acid. Its structure, therefore, is $COOH \cdot CH_2 \cdot COOH$.

When malonic acid is heated above its melting point, it decomposes quantitatively into acetic acid and carbon dioxide:

$$COOH \cdot CH_2 \cdot COOH \longrightarrow CO_2 + CH_3 \cdot COOH$$

This is an example of a general reaction. When a compound having two carboxyl groups attached to the same carbon atom is heated above its melting point, it yields carbon dioxide and leaves hydrogen in the place of one carboxyl.

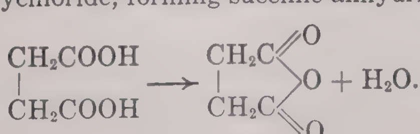
When heated with phosphorus pentoxide, malonic acid yields carbon suboxide and water as well as carbon dioxide and acetic acid. (See ketenes.)

SUCCINIC ACID

Succinic acid, $COOH \cdot CH_2 \cdot CH_2 \cdot COOH$ (m.p. 182°, b.p. 235°), occurs in amber, from which it may be obtained by distillation. It is formed in small amounts as a by-product when alcohol is made by the fermentation of glucose. It is made from ethylene dibromide by a process that establishes its structure:

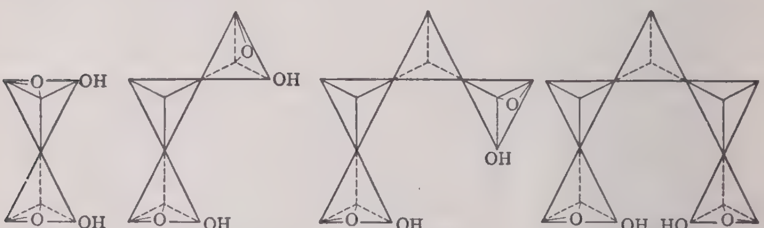
$$\begin{array}{l} CH_2Br \\ | \\ CH_2Br \end{array} \xrightarrow{2KCN} \begin{array}{l} CH_2CN \\ | \\ CH_2CN \end{array} \xrightarrow{4H_2O} \begin{array}{l} CH_2COOH \\ | \\ CH_2COOH \end{array}.$$

Succinic acid loses water, when heated with sulphuric acid or phosphorus oxychloride, forming succinic anhydride:



Isosuccinic acid, $CH_3 \cdot CH\begin{cases} COOH \\ COOH \end{cases}$, does not form an anhydride, but decomposes when heated above its melting point (130°) into carbon dioxide and propionic acid.

The fact that oxalic and malonic acids do not form true anhydrides, while succinic, glutaric, and adipic acids form them readily, is explained by a consideration of the three dimensional figures which would be formed by molecules made up of chains of two or more carbon atoms. Assuming, once more, that the carbon atom is a regular tetrahedron with its valence electrons stationed at the four apices, the acids mentioned may be represented graphically as follows:



Oxalic Malonic Succinic Glutaric

It will be observed that the hydroxyl groups that are involved in the anhydride formation approach each other as the number of carbon atoms increases from two to six. To link the first and fourth carbon atoms through oxygen by eliminating water involves less strain in the molecule than would be required to connect the first and second or the first and third carbon atoms. In consequence of this close approach of the hydroxyl groups, succinic acid can form an anhydride whereas oxalic and malonic cannot. The same sort of reasoning leads to the conclusion that glutaric and adipic acids should form anhydrides even more readily than does succinic, which is actually the case. As the number of carbon atoms increases above six or seven, anhydride formation should cause a strain in the opposite direction, and hence pimelic and suberic acids should not give up water so readily, and this corollary is supported by experimental evidence.

FUMARIC AND MALEIC ACIDS

Fumaric and maleic acids are unsaturated compounds corresponding to the formula $C_4H_4O_4$. Fumaric acid sublimes

at 200°. It is found in small quantities in many plants. It is not very soluble in water (1 : 160). Maleic acid is not found in nature. It is a synthetic product only. It melts at 130° and dissolves in less than twice its weight of water at 15°.

Fumaric and maleic acids are both obtained from malic acid, $COOH \cdot CHOH \cdot CH_2 \cdot COOH$, by eliminating one molecule of water, which is accomplished by heat alone. At 140° fumaric acid is formed; at 200° maleic acid is the chief product. Both have the structural formula $COOH \cdot CH : CH \cdot COOH$. They are geometrical isomers. (See p. 33.) The stereochemical structures are

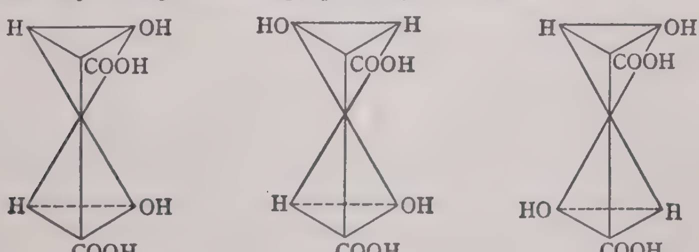
$$\begin{array}{rl} COOH \cdot & CH \\ & \| \\ & CH \cdot COOH \end{array} \quad \text{and} \quad \begin{array}{l} CH \cdot COOH \\ \| \\ CH \cdot COOH \end{array} .$$

Fumaric acid — Maleic acid

When heated, maleic acid yields an anhydride, one molecule of water being eliminated from the two carboxyl groups. Fumaric acid will not form an anhydride.

TARTARIC ACIDS

There are four tartaric acids corresponding to the formula $COOH \cdot CHOH \cdot CHOH \cdot COOH$. They present a very interesting case of stereoisomerism. The phenomenon of optical activity was considered in connection with the amyl alcohols (p. 49) and the cause was traced to an asymmetric structure of the molecule. Two of the tartaric acids are optically active and two inactive. Three structural formulas for tartaric acids may be represented graphically as follows:



I II III

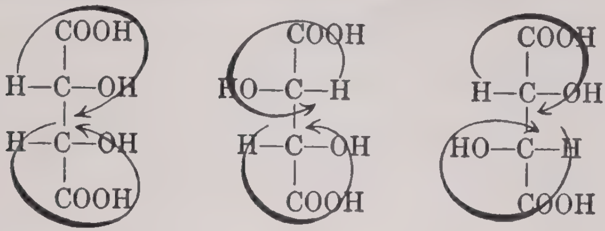
Imagine these tetrahedra flattened out on the plane of the paper, then the same configurations are represented by the simple projection formulas:

$$
\begin{array}{c}
\mathrm{COOH} \\
| \\
\mathrm{H{-}C{-}OH} \\
| \\
\mathrm{H{-}C{-}OH} \\
| \\
\mathrm{COOH} \\
\text{I}
\end{array}
\qquad\qquad
\begin{array}{c}
\mathrm{COOH} \\
| \\
\mathrm{HO{-}C{-}H} \\
| \\
\mathrm{H{-}C{-}OH} \\
| \\
\mathrm{COOH} \\
\text{II}
\end{array}
\qquad\qquad
\begin{array}{c}
\mathrm{COOH} \\
| \\
\mathrm{H{-}C{-}OH} \\
| \\
\mathrm{HO{-}C{-}H} \\
| \\
\mathrm{COOH} \\
\text{III}
\end{array}
$$

One of the inactive tartaric acids is a racemic compound consisting of a mixture of equal quantities of the mirror images represented by formulas II and III. The other inactive acid cannot be resolved into optically active forms; and must correspond to one of the three formulas given above. If formula I were cut in two between the asymmetric atoms, and if the lower half were rotated in the plane of the paper through an angle of 180°, it would appear as the mirror image of the upper half. If either of the other structures were severed and rotated in the same manner, the two halves would appear to be identical. In a structure of the type represented by formula II or III any effect the upper half of the molecule has on polarized light is duplicated by the lower half; but in a structure like formula I, if the upper half tends to turn the plane of polarization to the right, the lower half rotates it to the left, and since the two ends are similarly asymmetric, that is, identical groups are attached to both asymmetric carbon atoms, the gyratory power of one is exactly counterbalanced by the other. That is to say, the molecule is optically inactive on account of internal compensation. It is not racemic (that is, it is not a mixture of two active forms), but it is inactive on account of the equal and opposite effects produced by the two similarly asymmetric ends of the same molecule.

The question as to whether similar groups in a molecule will actually nullify or reënforce the optical properties of each other may be determined by inspection of the formula in another way. Suppose we pass around each asymmetric atom in such a way as to encounter the attached groups in a definite order, say, for example, H, COOH, OH, $C_2H_3O_3$, and let us indicate the path followed by means of an arrow. It will be observed that in formula I the course is clockwise around one and counter clockwise around the other asymmetric atom. The molecule is therefore inactive. In II the courses are both counter clock-

wise and in III both clockwise, and these forms are active, one being dextro-rotatory and the other lævo-rotatory.



I II III

Two dissimilar asymmetric carbon atoms in the same molecule give rise to four active stereoisomers and two racemic mixtures; but no internally compensated form.

Dextro-tartaric acid (m.p. 170°) is obtained from grapes. It occurs in grape juice in the form of a potassium salt, $KHC_4H_4O_6$ (cream of tartar), and precipitates when the juice ferments, on account of its insolubility in alcohol. This salt is used in connection with sodium bicarbonate in the manufacture of baking powders.*

$$KHC_4H_4O_6 + NaHCO_3 \longrightarrow KNaC_4H_4O_6 + H_2O + CO_2.$$

The sodium potassium salt, $NaKC_4H_4O_6$, known as Rochelle salt, is used in making Fehling's solution and in Seidlitz powder.

When *d*-tartaric acid is boiled with an excess of sodium hydroxide, it is racemized, that is, converted into an equimolecular mixture of the dextro and lævo forms. The racemic acid thus formed, *d-l*-tartaric, is optically inactive, but may be resolved into the active components by the methods devised by Pasteur (p. 136). Lævo-tartaric acid (m.p. 170°) is obtained by these methods from racemic acid. Mesotartaric acid, inactive on account of internal compensation, cannot be resolved into active components. It is formed along with racemic acid, when *d*-tartaric is boiled with a solution of sodium hydroxide.

* The leavening of bread is accomplished by releasing carbon dioxide in the dough. In some baking powders pure tartaric acid is used with sodium bicarbonate:

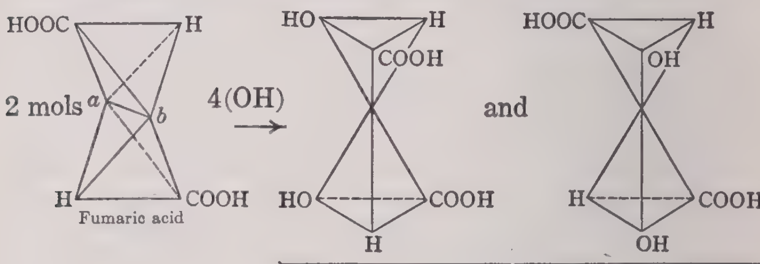
$$H_2C_4H_4O_6 + 2NaHCO_3 \longrightarrow Na_2C_4H_4O_6 + 2H_2O + 2CO_2.$$

In other powders alums or phosphates are substituted for the more expensive tartrate. The reactions of alum and phosphate powders are represented by the following equations:

$$K_2Al_2(SO_4)_4 + 6NaHCO_3 \longrightarrow 2Al(OH)_3 + 3Na_2SO_4 + K_2SO_4 + 6CO_2,$$
$$CaH_4(PO_4)_2 + 2NaHCO_3 \longrightarrow CaHPO_4 + NaH_2PO_4 + 2H_2O + 2CO_2.$$

Relationships existing between fumaric, maleic, succinic, and tartaric acids are easily interpreted on the basis of the structural formulas given above.

When maleic acid is oxidized by potassium permanganate, mesotartaric acid is formed. Fumaric acid under the same treatment yields a mixture of dextro- and lævo-tartaric acids (racemic). This is in strict harmony with the structure theory. The changes may be represented graphically as follows, but a clearer insight is obtained by means of models:

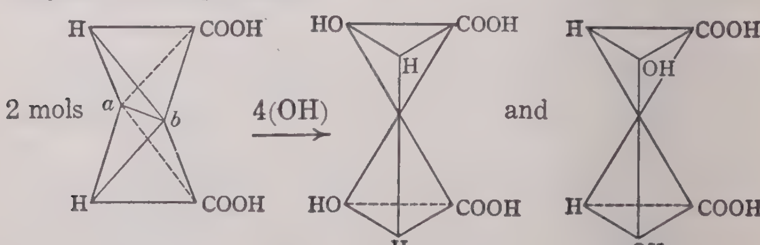


Fumaric acid

Racemic acid

The structure formed by breaking the double bond at position *a* and introducing at that point a hydroxyl group on each carbon is the mirror image of the product formed by breaking the bond at *b*. Since the chances for breaking at these two points are exactly equal, the two forms are produced in equal quantities.

When maleic acid is oxidized by the addition of two hydroxyl groups, the same structure is formed, no matter which position is attacked, and this structure corresponds to the one assigned to mesotartaric acid on the basis of its failure to yield to the method employed for resolving inactive compounds into optically active components.



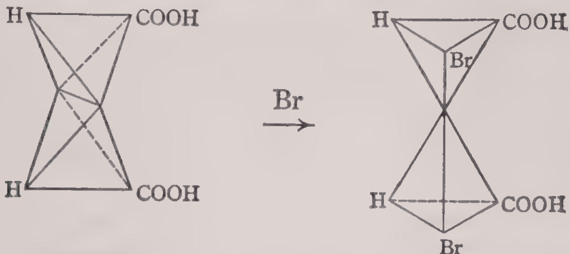
Maleic acid

Mesotartaric acid

Mesotartaric acid

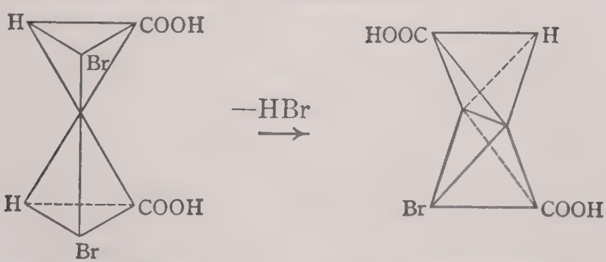
The principle of stereoisomerism accounts also for the results obtained when fumaric and maleic acids are treated with

bromine. Dibromsuccinic acids are formed in both cases, but they are not identical products. The dibromsuccinic acid made from maleic acid, when warmed with alcoholic potash, loses a molecule of hydrobromic acid and is thereby converted into bromfumaric acid. On the other hand, fumaric acid gives rise to a dibromsuccinic acid, which loses hydrobromic acid, with the formation of bromomaleic acid.



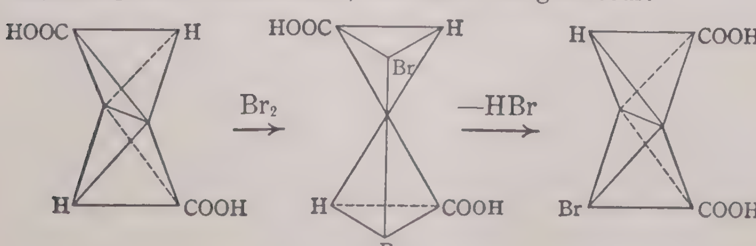
Maleic acid Iso-dibromsuccinic acid

Rotation around the common axis of the two tetrahedra, to bring the hydrogen on one carbon atom over bromine on the other, must occur before HBr can be eliminated. When this is accomplished, the double bond is established with the carboxyl groups on opposite sides of the molecule.



Iso-dibromsuccinic acid Bromfumaric acid

Beginning with fumaric acid, the same changes occur.



Fumaric acid Dibromsuccinic acid Brommaleic acid

Resolution of racemic acid. Three general methods are employed to resolve racemic mixtures into their optically active components.

1. Some microörganisms grow in racemic mixtures, destroying one isomer and leaving its enantiomorphic form unchanged. With the aid of *Penicillium glaucum,* Pasteur obtained lævo-tartaric acid from racemic acid. The dextro-rotatory form was removed by the organism.

2. In a few instances the two forms differ in crystalline structure, and may be separated by mechanical means. Quartz and sodium ammonium racemate, for example, produce crystals, some of which have right and others left hemihedral faces.

3. The best method from the standpoint of general application consists in forming condensation products with other optically active compounds. A racemic mixture forms two different derivatives with the same optically active reagents, and these derivatives may be separated by taking advantage of their differences in solubilities, boiling points, and so on. Such derivatives are not enantiomorphic, and hence they have different chemical and physical properties. Suppose, for example, we have a racemic acid composed of components $\overset{+}{A}$ and $\overset{-}{A}$. If we treat the mixture with a dextro-rotatory base, $\overset{+}{B}$, two different salts will be formed, $\overset{+}{A}\overset{+}{B}$ and $\overset{-}{A}\overset{+}{B}$. These may be separated, and subsequently decomposed, to yield the free acids $\overset{+}{A}$ and $\overset{-}{A}$. Pasteur accomplished the resolution of racemic acid with the aid of the lævo-rotatory base, cinchonine. The salt formed with the lævo-tartaric acid is much less soluble than the cinchonine *d*-tartrate.*

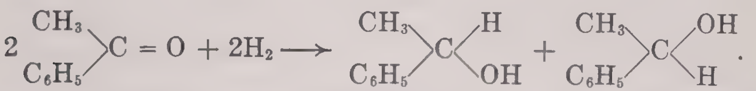
The optically active aldehyde, helicin, has been used to form condensation products with racemic amines. After separating the products by fractional crystallization, the helicin is split off by hydrolysis.†

Asymmetric synthesis. Attempts to prepare optically active compounds by synthetic methods without the aid of optically active reagents have failed. It is an easy matter to synthesize compounds having asymmetric carbon atoms, but there is always the same probability of obtaining one as the other of the active forms. As a result of this condition the

* Pasteur, *Ann. Chim. Phys.*, **38**, 437 (1853). Markwald, *Ber.*, **29**, 42 (1896).

† Erlenmeyer, Jr., *Ber.*, **36**, 976 (1903).

two forms are always produced in equal amounts and the synthetic product is racemic. Thus in the reduction of acetophenone, $CH_3 \cdot CO \cdot C_6H_5$, to $CH_3 \cdot CHOH \cdot C_6H_5$ the central carbon atom is rendered asymmetric, but there is no way to control the reaction so that one form will predominate in the mixture.



Acetophenone *d*-methyl-phenyl-carbinol *l*-methyl-phenyl-carbinol

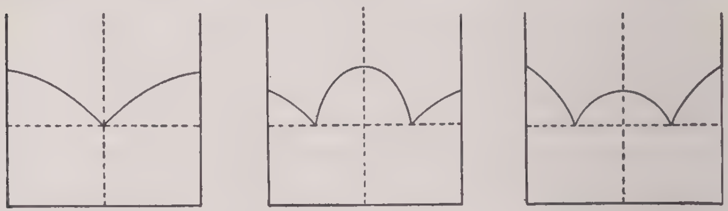
If, on the other hand, a new carbon atom is rendered asymmetric in a molecule which is already asymmetric and optically active, there may be a definite orientation of the entering groups favoring the formation of one of the enantiomorphic derivatives. This occurs in some reactions of *d*-glucose. The carbon atom of the aldehyde group is rendered asymmetric by addition of HCN, but the two stereoisomeric cyanhydrins are not formed in equal amounts.

Racemization. Many optically active compounds may be converted into mixtures of the two enantiomorphs by heating them alone or with acids or alkalies. *d*-Tartaric acid is racemized by heating with a little water in a sealed tube for five or six hours at 175°, or by boiling with a concentrated solution of sodium hydroxide.* The reaction takes place in two stages, mesotartaric acid being formed by rearrangement of two groups on one carbon atom, and the lævo-rotatory compound by a similar rearrangement involving both asymmetric atoms. This accounts for the fact that mesotartaric acid predominates in the early stages of the process, whereas racemic acid constitutes the final product. In many compounds having two or more asymmetric carbon atoms, the optically active forms are only partially racemized — the configuration with respect to one or more of the asymmetric groups remaining undisturbed. The interesting phenomenon of obtaining, through chemical reactions, a reversal in the sign of optical rotation is discussed under the Walden inversion.

In some cases a racemic product is not merely a mixture of the active enantiomorphs, but a compound of the two. Melting-point determinations and other applications of the phase rule may be made to distinguish be-

* Meissner, *Ber.*, **30**, 1574 (1897).

tween the two states. Although stereoisomers melt at the same temperature, mixtures of the two melt at a lower temperature, the minimum temperature corresponding to an equimolecular mixture — the racemic product. If the stereoisomers do not react with each other to form a definite compound, the melting-point curve produced by the addition of one active form to the other is represented in I. If the two forms produce a racemic compound, melting at a higher temperature than that of the components, the melting-point curve belongs to the type shown in II, and if it melts at



I II III

a lower temperature than the melting point of the enantiomorphic forms, the curve corresponds to III. In any case of compound formation, the melting-point of the pure compound is higher than that of a mixture of the compound with a small amount of either active form.

The addition of a small amount of one of the active modifications to the racemic product, therefore, elevates the melting point if the inactive substance is a mixture, and lowers the melting point if the product is a compound.

Optically active compounds of tin, silicon, sulphur, selenium, nitrogen, and phosphorus are known, and in every case it appears that four different radicals attached to the same atom are necessary and sufficient to give rise to stereoisomeric forms.

CYANIDES AND CYANATES

The principal derivatives of cyanogen are the cyanides or nitriles, RCN, the isocyanides or carbylamines, RNC, the cyanates, ROCN, isocyanates, RNCO, and the fulminates, RONC.

Cyanogen, C_2N_2 (m.p. $-34.4°$, b.p. $-20.7°$), is a colorless, poisonous gas, fairly soluble in water (4 : 1 by vol.), and very soluble in alcohol (23 : 1). It burns with a purple flame. Its formation from oxamide by dehydration indicates its structure:

$$\begin{array}{l} CONH_2 \\ | \\ CONH_2 \end{array} \xrightarrow{P_2O_5} \begin{array}{l} CN \\ | \\ CN \end{array} + 2H_2O.$$

It is usually made by heating a solution of potassium cyanide with copper sulphate. The cupric cyanide first formed decomposes, yielding cuprous cyanide and cyanogen.

Hydrogen cyanide or prussic acid, HCN (m.p. $-10°$, b.p. 25°), is a colorless, poisonous liquid, having an odor resembling that of almond oil. It has a high dielectric constant and is a good ionizing solvent for many inorganic salts. Prussic acid occurs as glucosides in bitter almonds and in the seeds of many tropical plants. It has been detected also in the smoke of cigars.* It is hardly as poisonous as is commonly supposed. For that reason, and also on account of its low density, it has not been used in gas warfare.†

As an acid, hydrocyanic is ten thousand times weaker than acetic. The dissociation constants are 1.3×10^{-9} and 1.8×10^{-5}, respectively. Its salts are decomposed by carbonic acid.

Many processes have been devised for using atmospheric nitrogen as a source of cyanides. Calcium carbide when

* Habermann, *Chemisches Centralblatt*, **1**, 53 (1903).

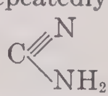
† To prove his theory that hydrocyanic acid is less poisonous to human beings than to lower animals Barcroft of England took a dog with him into a room in which the air contained a little hydrogen cyanide. After the dog had died Barcroft walked out of the room unharmed. A concentration of 0.1 mg. HCN per liter of air kills a dog in thirty minutes; 0.3 mg. per liter causes the death of a dog in less than ten minutes.

heated in an atmosphere of nitrogen is converted into calcium cyanide and calcium cyanamide:

$$CaC_2 + N_2 \longrightarrow Ca(CN)_2,$$
$$Ca(CN)_2 \longrightarrow CaNCN + C.$$

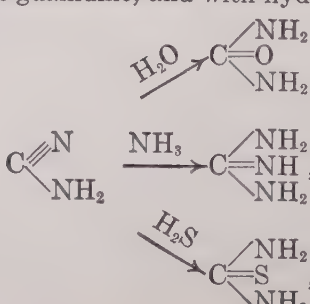
Calcium cyanamide is manufactured in enormous quantities for use as a fertilizer. When applied to the soil it undergoes hydrolysis to cyanamide, which in turn is converted into urea and ammonium salts. Under the influence of nitrifying bacteria present in all productive soils, ammonium salts are converted into nitrites and ultimately into nitrates, and thus nitrogen withdrawn from the air through the agency of calcium carbide becomes available to plants. Calcium carbide prepared from lime and coke in an electric furnace is pulverized, then reheated in an atmosphere of nitrogen. Enough heat is evolved in the reaction to maintain the nitrifying ovens at the proper temperature.

The nitrogen used is obtained from the atmosphere (1) by distillation of liquid air (the first fraction is largely nitrogen) or (2) by passing air over red-hot finely divided copper on asbestos. The copper oxide is reduced by hot natural gas without removing it from the tubes, so that the same copper can be used repeatedly.

Cyanamide, , is a colorless crystalline substance (m.p. 40°). The usual laboratory method for making it in small quantities consists in passing carbon dioxide over hot sodium amide:

$$2NaNH_2 + CO_2 \longrightarrow CNNH_2 + 2NaOH.$$

Cyanamide combines with water to form urea. With ammonia it yields guanidine, and with hydrogen sulphide it forms thiourea:



, Urea;

, Guanidine;

, Thiourea.

In an ammoniacal solution of a silver salt it forms a yellow precipitate $CN \cdot NAg_2$.

NITRILES

Potassium cyanide reacts with alkyl halides in alcoholic solution, yielding nitriles, RCN, mixed with smaller amounts of carbylamines or isonitriles, RNC*:

$$RX + KCN \longrightarrow R \cdot C \vdots N + KX;$$
$$RX + KCN \longrightarrow R \cdot N : C + KX.$$

The isonitriles are converted into the normal compounds when heated to 250°.

Nitriles are easily obtained from amides by heating the latter with phosphorus pentoxide:

$$CH_3 \cdot CONH_2 \xrightarrow{P_2O_5} CH_3 \cdot CN + H_2O.$$

If there are five or more atoms in the carbon chain of an amide, it may be converted into a nitrile by bromine and potassium hydroxide. An amine is first formed,† and with the lower members the amine is the final product; but longer chains are oxidized to nitriles.

$$C_5H_{11} \cdot CONH_2 + KOBr + 2KOH \longrightarrow C_5H_{11} \cdot NH_2 + K_2CO_3 + KBr + H_2O;$$
$$C_4H_9 \cdot CH_2NH_2 + 2KOBr \longrightarrow C_4H_9 \cdot CN + 2KBr + 2H_2O.$$

Aromatic cyanides are usually prepared by other methods.

The cyanides are readily hydrolyzed to amides or to acids. Boiling with acids or alkalies usually carries the hydrolysis to completion, that is to say, salts of acids are produced. Warming with hydrogen peroxide often results in the formation of amides:

$$R \cdot CN + H_2O_2 \longrightarrow R \cdot CONH_2 + \tfrac{1}{2}O_2;$$
$$R \cdot CN + 2H_2O \longrightarrow R \cdot COOH + NH_3.$$

Reduction by sodium amalgam in alcoholic solution or by any other source of nascent hydrogen converts a cyanide into an amine (Mendius reaction):

$$RCN + 2H_2 \longrightarrow RCH_2NH_2.$$

* Hydrocyanic acid is itself a tautomeric substance, $H \cdot C \vdots N$ and $H \cdot N : C$, and nearly all of its derivatives are capable of existence in two forms.

† See Beckmann Rearrangement.

These reactions all indicate that the carbon of the cyanide radical is linked directly to carbon in the alkyl group. In other words, the formula of a nitrile is RCN and not RNC.

Nomenclature. The nitriles are derived indirectly from alcohols or directly from alkyl halides and they are readily hydrolyzed to acids or reduced to amines. They are named with reference either to the alcohols from which they are derived or the acids which they form. Thus CH_3CN is either methyl cyanide or acetonitrile; and C_2H_5CN is ethyl cyanide or propionitrile.

CYANIDES OR NITRILES

Name	Formula	B.P.
Acetonitrile	CH_3CN	81.5°
Propionitrile	$CH_3 \cdot CH_2CN$	98°
Butyronitrile (*n*)	$CH_3 \cdot CH_2 \cdot CH_2 \cdot CN$	118°
Butyronitrile (iso)	$(CH_3)_2CHCN$	107°
Valeronitrile (*n*)	$CH_3(CH_2)_3CN$	141°
Isopropylacetonitrile	$(CH_3)_2CH \cdot CH_2CN$	129°
Methylethylacetonitrile	$\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>\!CHCN$	125°
Trimethylacetonitrile	$(CH_3)_3CCN$	106°
Isobutylacetonitrile	$(CH_3)_2CH \cdot CH_2 \cdot CH_2CN$	154°
Diethylacetonitrile	$(C_2H_5)_2CHCN$	146°

Methyl cyanide, $CH_3 \cdot CN$ (m.p. $-41°$), a liquid having a pleasant odor, is prepared by distilling acetamide with phosphorus pentoxide. Ethyl cyanide, $C_2H_5 \cdot CN$ (m.p. $-103°$), is made in the same way from the amide of propionic acid. All members of the series containing fewer than five carbon atoms and most of the higher members are liquids somewhat lighter than water and only sparingly soluble in water. Trimethylacetonitrile is a solid (m.p. 16°). Myristonitrile, $C_{13}H_{27}CN$, melts at 19°; palmitonitrile, $C_{15}H_{31}CN$, at 29°; stearonitrile, $C_{17}H_{35}CN$, at 41°; and margaronitrile or cetyl cyanide, $C_{16}H_{33}CN$, melts at 53°.

Carbylamines

The isocyanides or carbylamines are liquids characterized by persistent and offensive odors. They are produced from primary amines by the action of chloroform and an alkali in alcoholic solution:

$$CH_3 \cdot NH_2 + CHCl_3 \longrightarrow CH_3 \cdot NC + 3HCl.$$

Cold dilute acids hydrolyze carbylamines to amines and formic acid: $CH_3 \cdot NC + 2H_2O \longrightarrow CH_3 \cdot NH_2 + H \cdot COOH.$

They are not hydrolyzed by alkalies even when warmed. The normal cyanides, on the other hand, are hydrolyzed by either acids or alkalies.

The formula, R—N=C, for an isocyanide was established by Nef.* It was formerly written R—N≣C, but there is no evidence for the existence of a quadruple bond between atoms in any compound; and there is an abundance of evidence for the existence of compounds of bivalent carbon. That the carbon atom is unsaturated in an isocyanide is indicated by the fact that phenylisocyanide, $C_6H_5—N=C$, forms an addition product with chlorine, having the structure, $C_6H_5N=C\begin{matrix} \diagup Cl \\ \diagdown Cl \end{matrix}$; and is oxidized to an isocyanate by mercuric oxide:

$$C_6H_5—N=C + HgO \longrightarrow C_6H_5—N=C=O + Hg.$$

In these reactions additions occur on the carbon atom exclusively, and there are many other examples of the same type. If a multiple bond were broken, the added atoms would be shared by two elements instead of going to one alone. The addition in the case cited results merely in the conversion of bivalent carbon into the saturated tetravalent state.

CYANIC ACID

Cyanic acid, HOCN, derived from cyanuric acid, $(HOCN)_3$, as explained in the next paragraph, is an extremely unstable liquid. At temperatures above zero it polymerizes to an amorphous solid composed of cyamelide, $(HNCO)_3$, and cyanuric acid, $(HNCO)_3$. A solution of the acid in water is also unstable, changing spontaneously at ordinary temperatures into carbon dioxide and ammonia.

Cyanuric acid is made by heating urea. Biuret is first formed, but this reacts with another molecule of urea, forming cyanuric acid:

$$2\underset{\text{Urea}}{NH_2 \cdot CO \cdot NH_2} \longrightarrow \underset{\text{Biuret}}{NH_2 \cdot CO \cdot NH \cdot CO \cdot NH_2} + NH_3,$$

$$\underset{\text{Biuret}}{NH_2 \cdot CO \cdot NH \cdot CO \cdot NH_2} + \underset{\text{Urea}}{NH_2 \cdot CO \cdot NH_2} \longrightarrow \underset{\text{Cyanuric acid}}{C_3H_3N_3O_3} + 2NH_3.$$

* Nef. Annalen, **270**, 267 (1892); *ibid.*, **287**, 265 (1895).

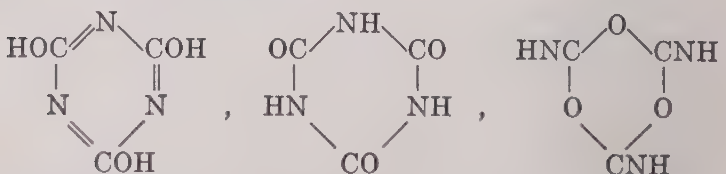
Cyanic acid is obtained by distilling cyanuric acid and cooling the distillate to a temperature below zero.

The constitution of cyanic acid has not been definitely established. It is either H—O—C≡N or H—N=C=O or an equilibrium mixture of the two. It forms two series of derivatives, those corresponding to the formula HOCN, called normal cyanates, and derivatives of HNCO, known as isocyanates. Esters of normal cyanic acid have not been isolated, for they polymerize as rapidly as formed, producing esters of cyanuric acid. Esters of isocyanic acid are well known. They are liquids having disagreeable odors. They polymerize to isocyanuric esters when heated and are hydrolyzed by water to carbon dioxide and amines:

$$RNCO + H_2O \longrightarrow RNH_2 + CO_2.$$

Normal cyanuric esters are called " O-esters," for in them the alkyl or aryl radicals are linked to oxygen. The *iso*- compounds are known as " N-esters."

Cyamelide, mentioned above as one of the polymerization products of cyanic acid, is a stable, non-volatile, and insoluble solid substance. It is formed rapidly and spontaneously from the vapor of cyanic acid at ordinary temperatures. At higher temperatures cyanuric acid is formed. Cyamelide is converted into cyanuric acid by hot alkalies; but cyanuric acid can be changed back to cyamelide only through the formation of cyanic acid as an intermediate product. The formulas assigned to these substances are



Cyanuric acid, *iso*-Cyanuric acid, Cyamelide

But there is still doubt as to the validity of these structures.

FULMINIC ACID

Fulminic acid, H—O—N=C, has not been isolated in the free state. Its salts are more stable and have been carefully investigated. But even the salts of fulminic acid must be handled with care. They are easily detonated, and in fact their only

practical value depends upon this property. Mercury fulminate is used in percussion caps for firearms and in the caps used in connection with fuses for firing blasting gelatine and dynamite.

A direct determination of the molecular weight of fulminic acid is impossible; but by indirect methods* it has been definitely proved that its value is approximately 43. From a consideration of the decomposition products (which consist almost exclusively of compounds containing only one carbon atom), and from a study of the addition products of fulminic acid, Nef† produced satisfactory evidence that the formula is HONC, and the double formula, $H_2C_2N_2O_2$, formerly used, has been abandoned. The unwillingness of many chemists to concede the existence of compounds of bivalent carbon delayed for a time the acceptance of Nef's formula.

Fulminic acid forms an addition product, methyl nitrolic acid, with nitrous acid. The reaction is reversible:

$$\mathrm{H{-}O{-}N{=}C + HNO_2 \rightleftarrows H{-}O{-}N{=}C\langle{}^{H}_{NO_2}}.$$

Methyl nitrolic acid is an intermediate product formed in the process of making mercury fulminate by the action of mercury on a mixture of nitric acid and alcohol. Any mercuric salt acts upon methyl nitrolic acid to yield mercury fulminate:

$$\mathrm{Hg(NO_3)_2 + 2HONCH(NO_2)} \longrightarrow \underset{\text{Mercury fulminate}}{\mathrm{Hg\langle{}^{ONC}_{ONC}}} + \mathrm{2HNO_3 + 2HNO_2}.$$

Hydrochloric acid combines with fulminic acid, yielding the oxime of formyl chloride in the form of large, colorless crystals which rapidly vanish by evaporation, even at room temperature:

$$\mathrm{H{-}O{-}N{=}C + HCl \longrightarrow H{-}O{-}N{=}C\langle{}^{H}_{Cl}}.$$

This reaction, coupled with the fact that fulminic acid and many of its derivatives yield hydroxylamine on hydrolysis,

* Wohler, *Ber.*, **38**, 1351 (1905).
† Nef, *Ann.*, **280**, 303 (1894).

indicates the presence of the =NOH group in all of those compounds.

The formation of benzaldoxime from mercury fulminate, partially hydrated aluminum chloride, and benzene is explained on the basis of Nef's formula as follows:

Hydrogen chloride liberated from hydrated aluminum chloride forms formyl chloride oxime, as indicated by the equation given above. This reacts with benzene * forming benzaldoxime, and the latter is hydrolyzed to benzaldehyde and hydroxylamine.

* Friedel and Crafts reaction.

THE AMMONIA SYSTEM

Franklin* has called attention to remarkable analogies between the properties of water and ammonia; and has developed what is known as the ammonia system of acids, bases, and salts. Water and liquid ammonia are good ionizing solvents. Each is characterized by a high dielectric constant, high specific heat, high heat of vaporization, and low boiling-point elevation constant. Ionic reactions may be carried out in liquid ammonia as well as in water, and the concentration law applies as well to reactions in liquid ammonia as in any other solvent. For instance, silver chloride is precipitated from an aqueous solution of silver nitrate and barium chloride, because of the insolubility of silver chloride in water. In liquid ammonia silver chloride, silver nitrate, and barium nitrate are soluble, and barium chloride is insoluble. The equation,

$$2AgNO_3 + BaCl_2 \rightleftharpoons 2AgCl + Ba(NO_3)_2,$$

represents a typical double decomposition which proceeds from left to right in water or from right to left in liquid ammonia.

The ordinary oxygen acids are considered as derivatives of water in which hydrogen has been replaced by a non-metallic element or by a negative radical. Acetic acid, for example, is water in which the hydrogen atom has been replaced by the acetyl group, CH_3CO—. If the same group is substituted for hydrogen in ammonia, we obtain the amide, CH_3CONH_2, or the imide, $(CH_3CO)_2NH$, and these are acids in the ammonia system. That is to say, they bear the same relationship to ammonia that ordinary acids bear to water.

Bases, such as $NaOH$ and $Ba(OH)_2$, are derivatives of water in which hydrogen atoms have been replaced by metals. Similarly, compounds like sodium amide, $NaNH_2$, and barium imide, $BaNH$, represent derivatives of ammonia in which hydrogen atoms have been replaced by metals. They are bases in the ammonia system.

* Franklin, *Am. Chem. J.*, **47**, 285 (1912); *J. Am. Chem. Soc.*, **37**, 2279 (1915); *ibid.*, **46**, 2137 (1924).

Ordinary acids and bases react to form salts and water; and in the same way, ammono acids and bases yield ammono salts and ammonia:

$$\underset{\text{Aquo acid}}{CH_3COOH} + \underset{\text{Aquo base}}{NaOH} \rightleftharpoons \underset{\text{Salt}}{CH_3COONa} + \underset{\text{Solvent}}{H_2O};$$

$$\underset{\text{Ammono acid}}{CH_3CONH_2} + \underset{\text{Ammono base}}{NaNH_2} \rightleftharpoons \underset{\text{Salt}}{CH_3CONHNa} + \underset{\text{Solvent}}{NH_3}.$$

Acid amides and imides are the acids of the ammonia system. Metallic amides, imides, and nitrides are the bases; and metallic derivatives of the acid amides and imides are the corresponding salts.

Alcohols, phenols, and ethers are derived from water by the substitution of radicals for hydrogen. In the ammonia system the aliphatic and aromatic amines represent similar types of substitution products. The analogies may be extended to substituted amines and phenols. Thus trinitrophenol (aquo picric acid), in aqueous solution, is a fairly strong acid, and trinitroaniline (ammono picric acid), dissolved in liquid ammonia, is an excellent conductor of electricity.

An ester is formed, in the water system, through the action of an acid on an alcohol, and by hydrolysis the ester may be reconverted into the original acid and alcohol, the reaction being reversible:

$$\underset{\text{Acid}}{RCOOH} + \underset{\text{Alcohol}}{R'OH} \rightleftharpoons \underset{\text{Ester}}{RCOOR'} + \underset{\text{Water}}{H_2O}.$$

In the ammonia system, the corresponding reagents and products are amides, amines, substituted amides (ammono esters), and ammonia; and the process of reconverting the ammono ester into the ammono acid and amine is called ammonolysis:

$$\underset{\text{Acid}}{RCONH_2} + \underset{\text{Alcohol}}{R'NH_2} \rightleftharpoons \underset{\text{Ester}}{RCONHR'} + \underset{\text{Ammonia}}{NH_3}.$$

Urea is ammono carbonic acid in the same sense that acetamide is ammono acetic acid, and Franklin and Stafford prepared potassium salts of urea, indicating that it actually displays acid properties.* Another ammono carbonic acid is cyanamide. Calcium cyanamide as an ammono salt corresponds, therefore, to the aquo salt calcium carbonate. Both of these salts may be made from calcium carbide, one by treatment with oxygen

* Franklin and Stafford, *Am. Chem. J.*, **28**, 83 (1902).

and the other through the action of nitrogen at high temperatures:

$$CaC_2 + 2O_2 \longrightarrow CaCO_3 + CO;$$
$$CaC_2 + N_2 \longrightarrow CaCN_2 + C.$$

When treated with steam, calcium ammono-carbonate is hydrolyzed to calcium aquo-carbonate:

$$CaCN_2 + 3H_2O \longrightarrow CaCO_3 + 2NH_3.$$

At higher temperatures the reaction is reversed, the ordinary calcium carbonate being ammonolyzed:

$$CaCO_3 + 2NH_3 \longrightarrow CaCN_2 + 3H_2O.$$

The corresponding derivatives of hydrogen sulphide are thio acids, bases, and salts, thio alcohols, and so on.

Reactions between the members of either of these series are not necessarily confined to the solvent from which they are derived; but it is not always possible to carry out the same reaction in water, ammonia, and in hydrogen sulphide. Thus acetic acid and potassium hydroxide form potassium acetate and water, whether the solvent is water or liquid ammonia. Acetic acid and potassium amide yield potassium acetate and ammonia, when the solvent is liquid ammonia. In water KNH_2 is rapidly hydrolyzed to KOH and NH_3, hence the reactions in the two solvents are not comparable, and in liquid hydrogen sulphide these reagents are insoluble.

THE CARBOHYDRATES

From the standpoint of plant life the carbohydrates are the most important compounds in nature; for the major part of the solid matter in all plant tissues is made up of representatives of this group. Cellulose, starch, and sugar are typical carbohydrates.

The name implies that these compounds are hydrates of carbon; it was, in fact, chosen to convey that idea. Sugars are now known, however, in which hydrogen and oxygen are not present in exactly the same ratio as in water. Examples are rhamnose and fucose, each having the formula $C_6H_{12}O_5$. On the other hand, there are many compounds consisting of carbon, hydrogen, and oxygen, with formulas of the type $C_nH_{2n}O_n$, that are not related to the sugars and would never be classed as carbohydrates on the basis of physical or chemical properties. Examples are formaldehyde (CH_2O), acetic acid ($C_2H_4O_2$), and lactic acid ($C_3H_6O_3$).

We now define the carbohydrates as aldehyde-alcohols or ketone-alcohols, or compounds which, by hydrolysis, yield aldehyde-alcohols or ketone-alcohols. We divide them arbitrarily into two principal classes: (1) the crystalline, soluble, and sweet carbohydrates of comparatively low molecular weights known as sugars, and (2) the amorphous, tasteless, and more or less insoluble bodies called celluloses and starches.

The carbohydrates are classified also as monosaccharides, disaccharides, and polysaccharides. The monosaccharides include the simple sugars, such as glucose and fructose, and all carbohydrates that cannot be hydrolyzed with the production of smaller units. The disaccharides, such as cane sugar, milk sugar, and maltose, are carbohydrates that are made up of two smaller carbohydrate molecules, and each polysaccharide is composed of more than two monosaccharide molecules and can be resolved into these simpler units by hydrolysis.

Although the only important monosaccharides are the sugars having five or six carbon atoms in the molecule, representatives

of the class are known with from two to ten carbon atoms. The names biose, triose, tetrose, pentose, and so on are used to designate these sub-classes. The terms aldose and ketose are used to distinguish the aldehyde-alcohols from the ketone-alcohols. Thus, if a monose is a ketone alcohol of six carbon atoms, it is called a keto-hexose; an aldehyde-alcohol of five carbon atoms is an aldo-pentose.

GLUCOSE

Dextrose (*d*-glucose or grape sugar), a colorless, crystalline sugar, is present in most fruits, either in the free state or as a constituent of polysaccharides. It is obtained with an equivalent amount of *d*-fructose when cane sugar is hydrolyzed. It is the ultimate hydrolysis product of starch and glycogen. It is made from corn starch in enormous quantities for use in sirups and in confections. Dextrose crystallizes from water in hexagonal plates, containing one molecule of water and melting at 86°. From alcohol it crystallizes in anhydrous needles, melting at 146°. It is dextro-rotatory $[\alpha]_D = 52.7°$.*

A freshly prepared aqueous solution of hydrated dextrose has a specific rotation of 105.2°, and a freshly prepared solution of the anhydrous sugar has a rotation of 22.5°. Both solutions gradually change in rotatory power until the normal value (52.7°) is reached. The phenomenon of change in this optical property is called mutarotation. It is displayed by a great variety of compounds, and is due to the slow establishment of

* The specific rotation of a compound, $[\alpha]_D$, is the angle of rotation of plane polarized light of wave length corresponding to the yellow sodium line in the solar spectrum when it traverses 10 cm. of a solution of the compound at 20° C., the concentration of the solution being one gram of the solute per cubic centimeter of solution. Such a concentration cannot ordinarily be obtained, but the theoretical rotation under such conditions may be calculated from observations of the rotation produced in any solution of known concentration.

$$[\alpha]_D = \frac{av}{lw}.$$

In this equation a is the observed rotation (deg.), v the volume of solution (cc.), l the length of the column (dm), and w the weight of the dissolved substance (g). For optically active liquids:

$$[\alpha]_D = \frac{a}{ld}.$$

In this case d is the density of the liquid $\left(\frac{g}{cc}\right)$.

equilibrium between tautomeric forms of the dissolved substance.

The preliminary steps in the determination of the structure of dextrose are based upon the following reactions which are common to all aldo-hexoses.

1. By analysis and molecular-weight determinations dextrose is found to have the empirical formula $C_6H_{12}O_6$.

2. It is reduced by sodium amalgam to *d*-sorbitol and by hydrogen iodide to normal secondary hexyl iodide. Sorbitol is a hexatomic alcohol which also yields normal secondary hexyl iodide when reduced with hydrogen iodide. The iodide has the formula $CH_3 \cdot CH_2 \cdot CHI \cdot CH_2 \cdot CH_2 \cdot CH_3$; for with silver hydroxide it yields a secondary alcohol which on oxidation gives the ketone $CH_3 \cdot CH_2 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH_3$. The formula of the ketone is known from the fact that it can be oxidized to acetic and normal butyric acids. Therefore, the six carbon atoms in glucose form a continuous chain,

$$\begin{array}{ccccccccccccc} & | & & | & & | & & | & & | & & | & \\ — & C & — & C & — & C & — & C & — & C & — & C & —. \\ & | & & | & & | & & | & & | & & | & \end{array}$$

3. Dextrose forms an addition product with one and only one molecule of hydrogen cyanide. It forms an oxime with hydroxylamine and a hydrazone with phenylhydrazine. It, therefore, has one carbonyl group. It is either an aldehyde or a ketone.

4. Gentle oxidation converts dextrose into a monobasic acid (gluconic acid), $C_6H_{12}O_7$, having the same number of carbon atoms. At the same time the properties referred to in the last paragraph disappear. The sugar is, therefore, an aldehyde, and since the group CHO is univalent, the carbon atom in this group is terminal, that is, it is at the end of the chain.

5. Gluconic acid is oxidized by nitric acid, the product being the dibasic saccharic acid ($C_6H_{10}O_8$). Dextrose has, therefore, a primary alcohol group, for, by oxidation, two carboxyl groups are formed without loss of carbon, and only one aldehyde group is present in the unoxidized molecule. This CH_2OH group, being univalent, must be terminal. We have then

$$\begin{array}{ccccccccccccc} & & H & & & & & & & & & & H \\ & & | & & | & & | & & | & & | & & | \\ H & — & C & — & C & — & C & — & C & — & C & — & C{=}O. \\ & & | & & | & & | & & | & & | & & \\ & & OH & & & & & & & & & & \end{array}$$

6. Dextrose reacts with acetic anhydride or acetyl chloride, forming a penta-acetyl derivative, indicating the presence of five hydroxyl groups. Stable compounds having two hydroxyl groups attached to the same carbon atom are exceedingly rare; and the few that exist behave like aldehydes. The hexahydric alcohol derived from glucose, by reduction, has no aldehydic properties. Hence we must conclude that only one hydroxyl group is attached to each of five carbon atoms:

$$\begin{array}{cccccc} \mathrm{H} & & & & & \mathrm{H} \\ | & | & | & | & | & | \\ \mathrm{HC}- & \mathrm{C}- & \mathrm{C}- & \mathrm{C}- & \mathrm{C}- & \mathrm{C{=}O.} \\ | & | & | & | & | & \\ \mathrm{OH} & \mathrm{OH} & \mathrm{OH} & \mathrm{OH} & \mathrm{OH} & \end{array}$$

The empirical formula ($C_6H_{12}O_6$) indicates that four other hydrogen atoms are present in the molecule, and it is obvious that they must be held by the four central carbon atoms. The formula, therefore, for dextrose and for any aldohexose must be

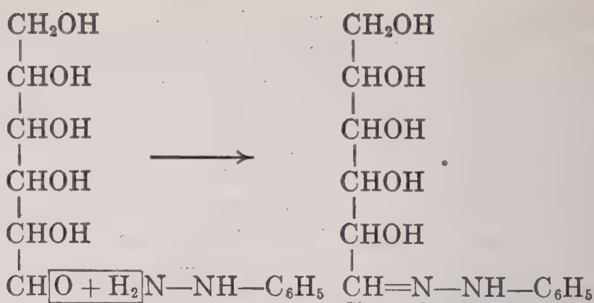
$$CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHO.$$

There are four asymmetric carbon atoms, and sixteen stereoisomeric compounds having this structure should exist.* Fourteen of them are known. The complete structure of dextrose or of any of its isomers cannot be written until we have determined the relative positions, in space, of the groups surrounding each of the asymmetric carbon atoms. Evidence bearing upon this point is presented later (p. 160).

Chemical properties. Some of the reactions of dextrose have been mentioned; namely, its susceptibility to oxidation and reduction, its reactions with acetyl chloride, hydrogen cyanide, hydroxylamine, and phenylhydrazine. The latter deserves further consideration, and a few other reactions must be mentioned.

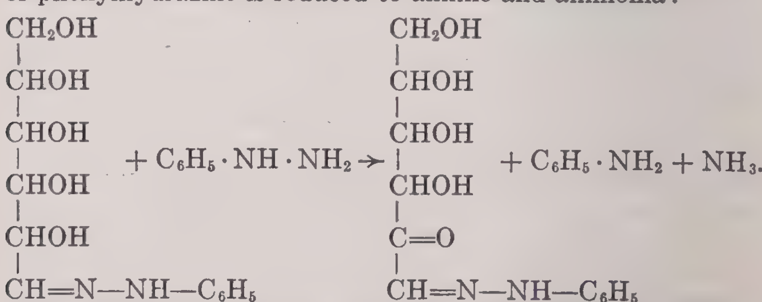
Phenylhydrazine acts upon dextrose, as it does upon any aldehyde, forming a hydrazone and water:

* Let n represent the number of asymmetric carbon atoms in a molecule, a the number of optically active forms, c the forms that are inactive due to internal compensation, and r the racemic forms; then (1) if the molecule cannot be divided into similar halves, $a = 2^n$; $c = 0$; (2) if n is even and the molecule forms similar halves, $a = 2^{n-1}$; $c = 2^{\frac{n}{2}-1}$; (3) if n is odd and the formula yields similar halves by excluding the middle carbon atom, $a = 2^{n-1} - 2^{\frac{n-1}{2}}$; $c = 2^{\frac{n-1}{2}}$. (r always equals $\frac{a}{2}$.)

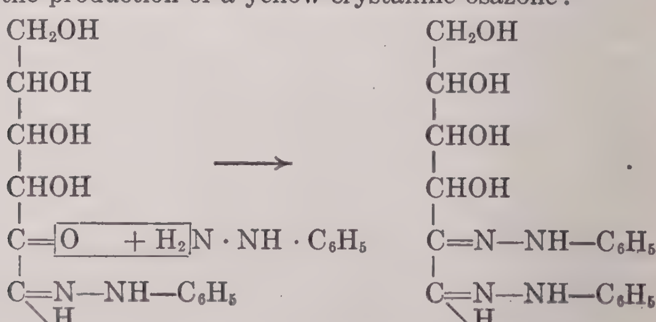


Glucose phenylhydrazone, m.p. 145°

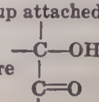
But in the presence of an excess of the reagent, two atoms of hydrogen are removed from the carbon atom adjacent to the aldehyde group, a keto-hydrazone is formed, and one molecule of phenylhydrazine is reduced to aniline and ammonia:*



A third molecule of phenylhydrazine then acts upon this ketone with the production of a yellow crystalline osazone:



Glucosazone, m.p. 205°

* In every carbohydrate molecule there is a hydroxyl group attached to a carbon atom which is adjacent to the carbonyl group. The structure  is common to all members of this class.

Further reduction of the compound cannot be accomplished by means of phenylhydrazine. The colors, crystal forms, and melting points of the osazones afford very satisfactory means of identifying the sugars.

Dextrose reduces an alkaline solution of copper sulphate (Fehling's solution), yielding a precipitate of cuprous oxide. The reaction is of clinical importance, — the usual method for detecting sugar in urine being based upon it. Metallic silver is precipitated when glucose acts upon an ammoniacal solution of silver nitrate.

Glucose is converted into alcohol and carbon dioxide through fermentation induced by an enzyme, zymase, which is found in yeast (p. 180).

FRUCTOSE

Lævulose (*d*-fructose, or fruit sugar) occurs combined with *d*-glucose in cane and beet sugar, and exists in the free state mixed with glucose and other substances in honey. It is the sole product obtained when inulin, a starch-like polysaccharide found in many plants, is hydrolyzed. It crystallizes in rhombic needles, melting at 95°. It is lævo-rotatory ($[\alpha]_D = -93°$). The prefix, *d*-, indicates its relationship to dextro glucose rather than the nature of its optical activity. Its structure is so related to that of *d*-glucose that either of these sugars may be converted into the other. In the same way we refer to *d*-gluconic acid and *d*-saccharic acid as oxidation products of *d*-glucose or dextrose. From *l*-glucose by oxidation we obtain *l*-gluconic and *l*-saccharic acid and by reduction *l*-sorbitol, and so on. The dextro- and lævo-glucose molecules are taken as the parent substances for hexose derivatives, and compounds derived from them have the prefixes *d* and *l*, regardless of the signs of their optical rotations.

Like glucose, fructose has the empirical formula $C_6H_{12}O_6$. It yields a penta-acetyl derivative, an oxime, and an osazone. The latter is identical with the product formed by the action of *d*-glucose on phenylhydrazine. Hence the structure of *d*-fructose differs from that of dextrose only in the orientation of groups attached to terminal and penultimate carbon atoms. Unlike glucose, it fails to yield an acid with the same carbon content when oxidized, but gives rise to two acids of lower molecular weight, namely, glycolic and trihydroxybutyric acids.

It is, therefore, a ketone. All of these reactions indicate that *d*-fructose has the structure

$$CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CO \cdot CH_2OH.$$

There are three asymmetric carbon atoms in the fructose molecule, and eight different keto-hexoses have this structure.

MANNOSE

Mannose is a constituent of a great variety of glucosides, but apparently does not exist in the free state as a natural product. It resembles glucose in general physical and chemical properties. With phenylhydrazine it yields a yellow crystalline osazone, identical with the osazones formed from glucose and fructose.

GALACTOSE

d-Galactose (m.p. 168°) is obtained, with an equal amount of glucose, by hydrolyzing milk sugar. It is an aldohexose, dextro-rotatory, and fermentable, under the influence of an enzyme occurring in some yeasts. Nitric acid converts it into mucic acid, $COOH \cdot (CHOH)_4 \cdot COOH$. The acid is optically inactive, due to intramolecular compensation and, therefore, cannot be resolved into active components.

Galactose is produced in sugar beets under unfavorable conditions of growth. It combines with sucrose in the beet, forming a trisaccharide, raffinose. Drought, frost, or any other factor that disturbs the normal development of the plant increases the yield of raffinose. Galactose occurs also in the glucosides known as saponins.

Configuration of the Monosaccharides

PENTOSES

The molecular formula for any pentose is $C_5H_{10}O_5$. As in the case of the hexoses these sugars are aldehyde-alcohols or ketone-alcohols, capable of being reduced to normal alcohols or straight chain hydrocarbons. Gentle oxidation converts the aldoses into monobasic and dibasic acids without loss of carbon, and the ketoses into acids of lower molecular weight. Acetyl chloride reacts with them to form tetra-acetyl derivatives. Hydrocyanic acid, hydroxylamine, and phenylhydrazine form cyanhydrins, oximes, and osazones, respectively, with

the pentoses, just as they do with the hexoses. The pentoses, therefore, have the structures

$$
\begin{array}{c}
CH_2OH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CHO \\ \text{Aldo-pentose}
\end{array}
\qquad \text{and} \qquad
\begin{array}{c}
CH_2OH \\ | \\ CHOH \\ | \\ CHOH \\ | \\ C{=}O \\ | \\ CH_2OH \\ \text{Keto-pentose}
\end{array}
.
$$

Eight isomeric aldo-pentoses and four keto-pentoses are known. Half of them are dextro-rotatory; the others are lævo-rotatory. The aldo-pentoses exist in four pairs and the keto-pentoses in two pairs, each pair consisting of sugars having identical properties, except with respect to the rotation of the plane of polarization of light, and differing in this respect only in the sign of the angle of rotation. They are pairs of mirror images. According to the structure theory four, and only four, such pairs can exist for the aldo-pentoses, as follows:

$$
\begin{array}{c}
CH_2OH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ CHO \\ \text{I}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CHO \\ \text{II}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ CHO \\ \text{III}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ CHO \\ \text{IV}
\end{array}
$$

$$
\begin{array}{c}
CH_2OH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ CHO \\ \text{V}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ CHO \\ \text{VI}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ CHO \\ \text{VII}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CHO \\ \text{VIII}
\end{array}
$$

The eight aldo-pentoses are known as *d*- and *l*-ribose, *d*- and *l*-xylose, *d*- and *l*-arabinose, and *d*- and *l*-lyxose. Each pair of structures, therefore, represents a dextro and a lævo form.

It is not possible to decide which member of the pair represents the dextro-rotatory compound; but it is possible to determine which pair of formulas should be assigned to the two arabinoses and which to the riboses, and so on. Let us, therefore, consider the chemical properties that differentiate these pairs; and to simplify the procedure we will keep in mind only one structure from each pair, say, formulas I, III, V, and VII.

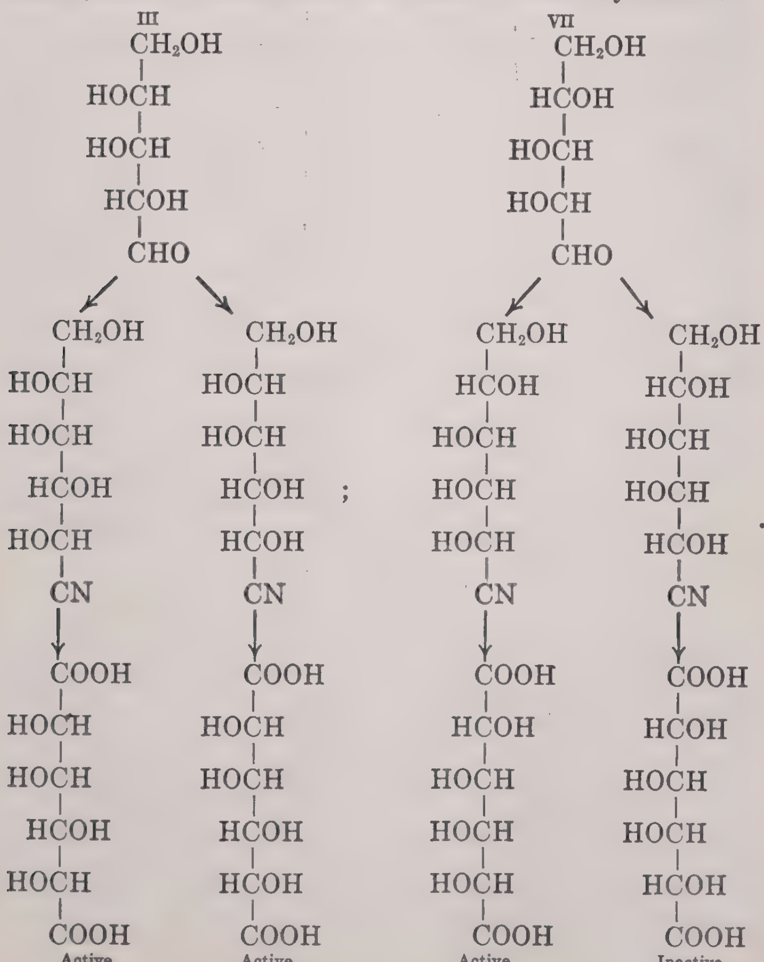
Arabinose and ribose react with phenylhydrazine to yield the same osazone. In forming an osazone from any aldehyde- or ketone-alcohol only the carbon atom of the carbonyl group and one adjacent to it become attached to phenylhydrazine residues. Hence, arabinose and ribose differ from each other only in the orientation of the groups attached to the carbon atom next to the aldehyde group. They are, therefore, either I and III or V and VII.

On oxidation, arabinose and lyxose yield trihydroxyglutaric acids, which are optically active; ribose and xylose yield inactive hydroxyglutaric acids. From the space formulas of these products it is easy to discern that the acids derived from I and V are inactive on account of intramolecular compensation (see p. 133), whereas the acids derived from III and VII are active:

	arabinose	xylose	
I	III	V	VII
CH_2OH	CH_2OH	CH_2OH	CH_2OH
HOCH	HOCH	HCOH	HCOH
HOCH	HOCH	HOCH	HOCH
HOCH	HCOH	HCOH	HOCH
CHO ;	CHO ;	CHO ;	CHO ;
↓	↓	↓	↓
COOH	COOH	COOH	COOH
HOCH	HOCH	HCOH	HCOH
HOCH	HOCH	HOCH	HOCH
HOCH	HCOH	HCOH	HOCH
COOH	COOH	COOH	COOH
Inactive	Active	Inactive	Active

Then arabinose and lyxose are represented by formulas III and VII, but it still remains to be determined which of the two structures should be assigned to either of them. Similarly, ribose is I or V, and xylose is either I or V.

The question as to whether arabinose is III or VII is settled by treating arabinose with hydrogen cyanide, hydrolyzing the cyanhydrin and oxidizing the resulting product to a dibasic acid. Under this treatment arabinose yields two different (isomeric) optically active acids. Lyxose under similar treatment yields one active and one inactive dicarboxylic acid.



Arabinose is thus proved to have formula III and lyxose VII. It follows from this conclusion that ribose is I, for arabinose and ribose yield the same osazone. It follows also that xylose is V, for lyxose and xylose form identical osazones.

HEXOSES

The sixteen possible stereochemical formulas of the aldohexoses are given in the following table:

CH_2OH	CH_2OH	CH_2OH	CH_2OH
HCOH	HCOH	HCOH	HOCH
HCOH	HCOH	HOCH	HOCH
HCOH	HCOH	HCOH	HCOH
HCOH	HOCH	HCOH	HOCH
CHO	CHO	CHO	CHO
I	II	III	IV

CH_2OH	CH_2OH	CH_2OH	CH_2OH
HOCH	HOCH	HOCH	HCOH
HOCH	HCOH	HCOH	HOCH
HCOH	HCOH	HCOH	HCOH
HCOH	HCOH	HOCH	HOCH
CHO	CHO	CHO	CHO
V	VI	VII	VIII

CH_2OH	CH_2OH	CH_2OH	CH_2OH
HOCH	HOCH	HOCH	HCOH
HOCH	HOCH	HCOH	HCOH
HOCH	HOCH	HOCH	HOCH
HOCH	HCOH	HOCH	HCOH
CHO	CHO	CHO	CHO
IX	X	XI	XII

XIII	XIV	XV	XVI
CH_2OH	CH_2OH	CH_2OH	CH_2OH
HCOH	HCOH	HCOH	HOCH
HCOH	HOCH	HOCH	HCOH
HOCH	HOCH	HOCH	HOCH
HOCH	HOCH	HCOH	HCOH
CHO	CHO	CHO	CHO

Formulas IX to XVI are mirror images of formulas I to VIII. We may, therefore, confine our attention to the first eight configurations.

By means of the cyanhydrin synthesis* the carbon chain in an aldose may be lengthened. Hydrocyanic acid forms an addition product with the aldehyde, thus introducing a new carbon atom, and at the same time rendering the carbon atom of the original aldehyde group asymmetric. The cyanide group is then hydrolyzed to carboxyl, and finally the resulting acid is reduced to an aldehyde by means of sodium amalgam.

In this way arabinose is converted into a mixture of glucose and mannose:

Arabinose		IV		V
CH_2OH		CH_2OH		CH_2OH
HOCH		HOCH		HOCH
HOCH	⟶	HOCH	and	HOCH
HCOH		HCOH		HCOH
CHO		HOCH		HCOH
		CHO		CHO

Glucose is, therefore, either IV or V and mannose is the other member of this pair.

Glucose and gulose, when oxidized, yield the same dicarboxylic acid. Hence it is evident that a transposition of the aldehyde and primary alcohol groups in glucose would result in

* Kiliani, *Ber.* **19**, 3033 (1914); *ibid.*, **21**, 916 (1916).

the formation of gulose. Transposing these groups in formula V would not change the structure of the molecule. The same transposition in IV would produce a different sugar. Formula IV, therefore, must be assigned to glucose, and V represents the structure of mannose. Since glucose and gulose yield the same dicarboxylic acid on oxidation, gulose has the structure represented in formula III.

Idose and gulose yield the same osazone. This relationship indicates that they differ only in the asymmetry of the carbon next to the carbonyl group. Hence idose has formula VIII.

Galactose, an aldohexose obtained from the hydrolysis products of milk sugar, yields optically inactive products when oxidized to a dicarboxylic acid, or reduced to a hexahydric alcohol. Of the four structures still unassigned only I and VII would be converted into inactive products by making the terminal groups alike. Galactose, therefore, is I or VII.

By introducing an additional carbon atom into the galactose molecule by means of hydrocyanic acid, hydrolyzing the cyanhydrin, and oxidizing this product, we obtain two active dicarboxylic acids (pentahydroxypimelic acids). Formula I gives rise to one active and one inactive product:

$$\begin{array}{ccccc}
\mathrm{CH_2OH} & & \mathrm{COOH} & & \mathrm{COOH} \\
| & & | & & | \\
\mathrm{HCOH} & & \mathrm{HCOH} & & \mathrm{HCOH} \\
| & & | & & | \\
\mathrm{HCOH} & & \mathrm{HCOH} & & \mathrm{HCOH} \\
| & \longrightarrow & | & \text{and} & | \\
\mathrm{HCOH} & & \mathrm{HCOH} & & \mathrm{HCOH} \\
| & & | & & | \\
\mathrm{HCOH} & & \mathrm{HCOH} & & \mathrm{HCOH} \\
| & & | & & | \\
\mathrm{CHO} & & \mathrm{HCOH} & & \mathrm{HOCH} \\
 & & | & & | \\
 & & \mathrm{COOH} & & \mathrm{COOH} \\
\text{I} & & \text{Inactive} & & \text{Active}
\end{array};$$

From VII two active products are obtained as indicated below. Hence the galactose formula is VII; and since galactose and talose yield the same osazone, talose must have formula VI. By the cyanhydrin synthesis *d*-ribose yields two hexoses having formulas I and II. They are called *d*-allose and *d*-altrose respectively. The corresponding derivatives of *l*-ribose (the mirror images of these two sugars) have not yet been prepared.

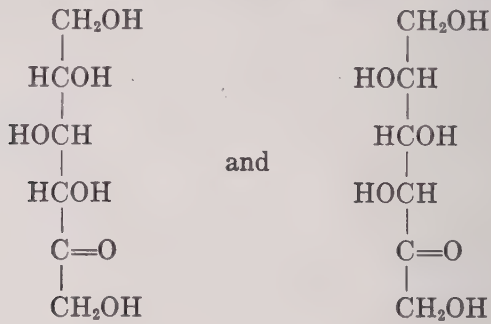
$$
\begin{array}{c}
CH_2OH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ CHO \\ \\ \text{VII}
\end{array}
\longrightarrow
\begin{array}{c}
COOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ COOH \\ \text{Active}
\end{array}
\quad \text{and} \quad
\begin{array}{c}
COOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ COOH \\ \text{Active}
\end{array}
$$

Assuming that formulas I to VIII represent the dextro-rotatory forms of the sugars, their mirror images (IX to XVI) must be assigned to the corresponding lævo-rotatory compounds. We have no means of ascertaining which formula in each pair actually belongs to the dextro-rotatory compound.

The ketoses are readily converted into derivatives of the aldoses. By identifying these derivatives of known structure, the configurations of the ketoses may be ascertained. For example, glucose and fructose yield the same osazone. The two sugars are alike in structure, therefore, with the exception of the grouping around the carbonyl carbon atom and one adjacent to it. In the aldose the carbonyl group is terminal. In the ketose it must be adjacent to the terminal carbon. With the glucose structure known, and the identity of the osazones of glucose and fructose established, the formula of fructose may be written:

$$
\begin{array}{c}
CH_2OH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ CHO \\ d\text{-Glucose}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ CHO \\ l\text{-Glucose}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HOCH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ C{=}O \\ | \\ CH_2OH \\ d\text{-Fructose}
\end{array}
\qquad
\begin{array}{c}
CH_2OH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ C{=}O \\ | \\ CH_2OH \\ l\text{-Fructose}
\end{array}
$$

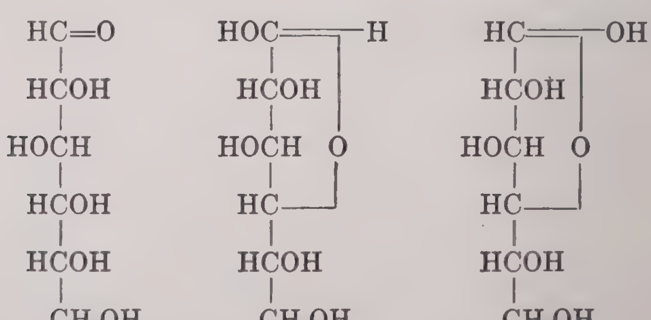
Sorbose, gulose, and idose yield the same osazone, indicating that *d*- and *l*-sorbose must be represented by the structures



MUTAROTATION

α AND β FORMS OF ALDOHEXOSES

It was mentioned above that *d*-glucose exhibits mutarotation. The phenomenon is not uncommon in connection with hydroxy aldehydes and hydroxy acids. To account for this property, and to explain at the same time the fact that the aldoses respond very slowly to aldehyde tests, it is assumed that each of the sixteen aldohexoses exist in two stereoisomeric forms of closed-chain structure. The closed-chain or lactone-like structures exist in solution in dynamic equilibrium with each other and with the straight-chain or ordinary aldehyde form:



d-Glucose (aldehyde form) α-*d*-Glucose β-*d*-Glucose

Closing the ring by a shift in the position of a hydrogen atom, as indicated here, renders the aldehyde carbon asymmetric and

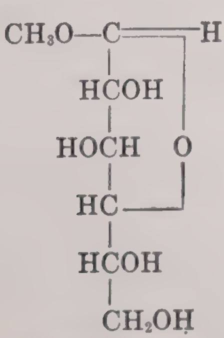
makes possible thirty-two instead of sixteen structures for the aldohexoses.

If these three forms exist in tautomeric equilibrium, it is obvious that glucose can act as if it were an aldehyde, but its activity as an aldehyde must depend upon the rate of transformation of the α and β modifications into the aldehyde form. The form of *d*-glucose having the highest rotatory power is referred to as the α-compound, $(\alpha)_D = 105.2°$; for β-*d*-glucose $(\alpha)_D = 22.5°$, and for an equilibrium mixture of the two forms $(\alpha)_D = 52.7°$. The addition of ammonia or of any alkali to a solution of either modification hastens the attainment of equilibrium.

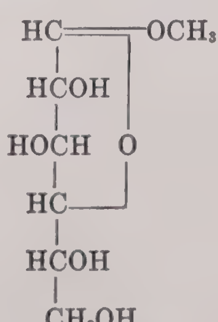
The hydroxyl on the γ-carbon atom is nearest to the aldehyde group (see p. 130), and it is reasonable to assume that the intramolecular reaction occurs between groups that are near each other, the resulting ring structure being thus formed without strain. Moreover, it is well known that γ-hydroxy acids form stable lactones. On the basis of these facts lactone formation in the aldehexoses is represented as a reaction involving the hydroxyl of the γ-carbon atom, but the possibility of the ring being closed at a different point is not excluded.

Instead of postulating the migration of a hydrogen atom between two points of attachment, many chemists prefer to regard the ring formation as due to the addition of a molecule of water to the aldehyde group, forming $-\mathrm{C}\!\begin{array}{l}\diagup\mathrm{H}\\-\mathrm{OH}\\\diagdown\mathrm{OH}\end{array}$, and subsequent elimination of water by a reaction between one of these hydroxyl groups and the hydroxyl of the γ-carbon atom.

Glucose reacts with methyl alcohol in the presence of hydrogen chloride, forming two stable isomeric glucosides. These compounds have no aldehydic properties.



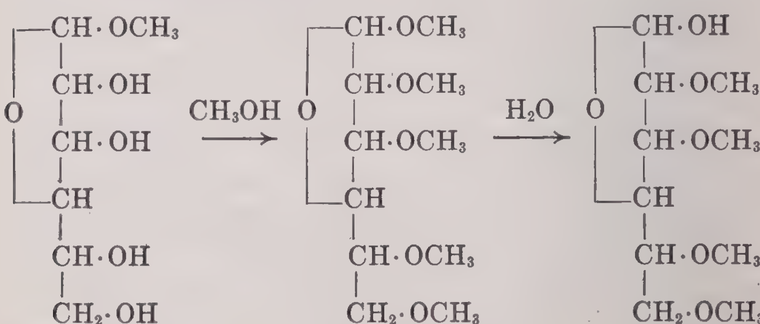
α-Methylglucoside



β-Methylglucoside

The aldehyde group of glucose, or the group which is potentially aldehydic, is involved in the formation of the methyl derivative. Moreover, the optical activity of a glucoside solution changes very slowly, if at all, on standing. In other words, the alkyl radical is less labile (less likely to shift its position) than is the corresponding hydrogen atom and the tautomeric glucose molecules give rise to stable isomeric methyl derivatives.

Methyl groups may be substituted for hydrogen in all of the hydroxyl groups. But if the completely methylated hexose be warmed with dilute hydrochloric acid, only one group is removed by hydrolysis. This, invariably, is the glucosidic methyl group. By these reactions we obtain from methyl glucoside 2, 3, 5, 6-tetramethylglucose.

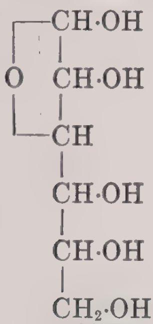


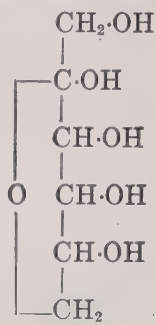
Methylglucoside — Tetramethyl Methylglucoside — 2, 3, 5, 6-Tetramethyl glucose

If groups that can be subsequently removed by hydrolysis are substituted for part of the hydroxyl hydrogen atoms in a sugar and the remaining free hydroxyl groups are methylated, the resulting product yields a partly methylated sugar when boiled with dilute hydrochloric acid. By this method Irvine* and his colleagues have prepared many of the possible methyl derivatives of glucose and fructose. With the structures of these compounds known, they have been able to determine the type of union that exists between these simple sugar units in the disaccharides, starches, and celluloses. The plan, in general, has been to methylate the complex carbohydrate, then to hydrolyze it, thereby breaking it up into methylated hexose molecules, and finally, to identify the hydrolysis products.

* J. C. Irvine, *J. Chem. Soc.*, **123**, 898 (1923).

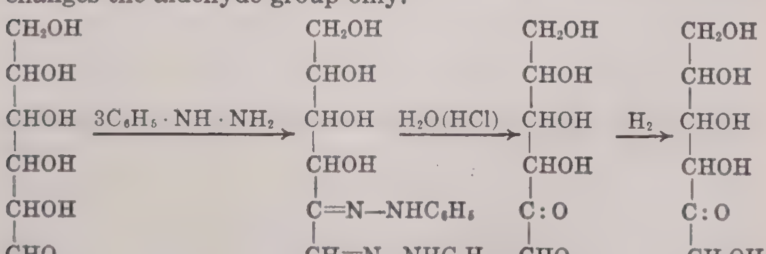
γ-Sugars. Some of the simple sugars and glucosides exist in forms that are not accounted for by assuming the existence of α and β isomers. They are additional isomers and are designated γ-sugars. Usually they are very reactive compounds. The free γ-sugars have never been isolated, but many glucosides derived from them are known. The isomerism is due to lactone formation in which an ethylene, propylene, or amylene oxide ring is formed. The α and β glucosides are characterized by the presence of the butylene oxide ring. To γ-glucose and γ-fructose Irvine assigns the following structures:


γ-Glucose


γ-Fructose

ALDOSES TO KETOSES

Aldoses may be converted into the corresponding ketoses by the following steps: (1) by the action of phenylhydrazine an osazone is formed; (2) fuming hydrochloric acid removes from the osazone both hydrazine groups and produces an osone; (3) the osone is reduced to a ketose. This is possible because an aldehyde is more easily reduced or oxidized than is a ketone. In the osone we have a ketone-aldehyde, and gentle reduction changes the aldehyde group only.


Aldose Osazone Osone Ketose

By this method fructose has been obtained from glucose.

KETOSES TO ALDOSES

Aldoses and ketoses are reduced by sodium amalgam to hexahydric alcohols. The terminal primary groups (CH_2OH) are more easily oxidized than the secondary groups (CHOH), and by selective oxidation the polyhydric alcohols may be converted into aldoses. In this manner glucose has been obtained from fructose.

$$
\begin{array}{ccccc}
CH_2OH & & CH_2OH & & CH_2OH \\
| & & | & & | \\
CHOH & & CHOH & & CHOH \\
| & & | & & | \\
CHOH & \xrightarrow{H_2} & CHOH & \xrightarrow{O_2} & CHOH \\
| & & | & & | \\
CHOH & & CHOH & & CHOH \\
| & & | & & | \\
CO & & CHOH & & CHOH \\
| & & | & & | \\
CH_2OH & & CH_2OH & & CHO \\
\text{Ketose} & & \text{Alcohol} & & \text{Aldose}
\end{array}
$$

At the same time products of more complete oxidation are formed. Glucose, for example, yields gluconic, glucuronic, and saccharic acids:

$$
\begin{array}{ccc}
CH_2OH & CHO & COOH \\
| & | & | \\
(CHOH)_4 & (CHOH)_4 & (CHOH)_4\,. \\
| & | & | \\
COOH & COOH & COOH \\
\text{Gluconic acid} & \text{Glucuronic acid} & \text{Saccharic acid}
\end{array}
$$

Either gluconic or saccharic acid may be made to predominate in the mixture by suitable choice of the oxidizing agent and proper control of the temperature. Bromine water is used to oxidize glucose to gluconic acid; but if saccharic acid is wanted, nitric acid is used. In either case a small quantity of glucuronic acid is formed.

Glucuronic acid is formed by the oxidation of glucose in the tissues and fluids of the animal organism, and, from the standpoint of physiological chemistry, it is a product of very great importance. The ordinary process of carbohydrate metabolism results in the oxidation of glucose to carbon dioxide and water; but with certain substances, which are not easily oxidized in the body, glucose forms stable compounds known as glucosides.

The unattached end of the glucose molecule is then oxidized to carboxyl, and the glucoside becomes a derivative of glucuronic acid. These derivatives of glucuronic acid are eliminated from the system in the urine. It is nature's way of removing from the animal organism such foreign substances as phenol, aniline, chloral, camphor, pinene, and many secondary and tertiary alcohols.

The conversion of glucose into fructose, and the reverse process, may be accomplished by allowing either sugar to stand for several days in alkaline solution. Mannose is formed simultaneously, and the three sugars remain in solution in equilibrium with each other. Wohl assumes that in the presence of an alkali the sugars exist largely in the enol form. In this form glucose, fructose and mannose become identical. Upon neutralizing the alkali, the carbonyl groups are reëstablished:

$$
\begin{array}{cccc}
CH_2OH & CH_2OH & CH_2OH & CH_2OH \\
| & | & | & | \\
HCOH & HCOH & HCOH & HCOH \\
| & | & | & | \\
HCOH & HCOH & HCOH & HCOH \\
| & | & | & | \\
HOCH & HOCH & HOCH & HOCH \\
| & | & | & | \\
HCOH & HOCH & CO & COH \\
| & | & | & \| \\
CHO & CHO & CH_2OH & CHOH \\
\text{Glucose} & \text{Mannose} & \text{Fructose} & \text{Enol form}
\end{array}
$$

It is not assumed that there is complete conversion to the enol form in solutions of bases, but that each of the three keto forms is in equilibrium with the common enol structure.

The Disaccharides

Disaccharides are carbohydrates which, on hydrolysis, yield two monose molecules. The only important disaccharides have the empirical formula $C_{12}H_{22}O_{11}$ and yield hexoses when hydrolyzed:

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow C_6H_{12}O_6 + C_6H_{12}O_6.$$

The two hexose molecules may be alike or different. The more important disaccharides are sucrose, lactose, and maltose.

SUCROSE

Sucrose, commonly called cane sugar, is obtained from sugar beets and from cane. It is present in considerable quantities in the sap of many trees including palms, birch, and the sugar maple. Flowers (the sources of honey) and ripe fruits are also natural repositories of this sugar.

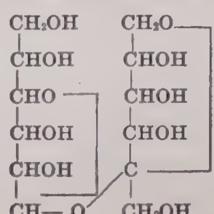
An enzyme, invertase, found in many yeasts and molds, catalyzes the hydrolysis of sucrose, the hydrolytic cleavage producing glucose and fructose in equal amounts. The equimolecular mixture of glucose and fructose (derived from dextro-rotatory cane sugar) is lævo-rotatory, and on account of the change in the direction of rotation, the mixture is often called invert sugar. Cane sugar does not undergo alcoholic fermentation, but glucose and fructose are both fermentable, the change being induced by an enzyme, zymase, found in yeast:

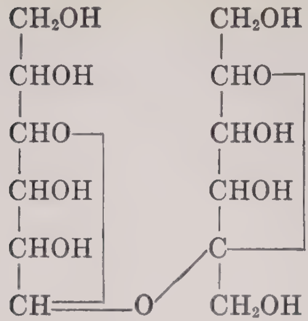
$$C_6H_{12}O_6 \longrightarrow 2C_2H_5OH + 2CO_2.$$

Some yeasts produce both invertase and zymase and, consequently, they are capable of converting sucrose into alcohol. The transformation is nevertheless accomplished in two distinct steps, each of which is brought about by a specific ferment.

Sucrose forms an octa-acetate, indicating the presence of eight hydroxyl groups. The fact that it is easily hydrolyzed to glucose and fructose justifies the conclusion that the two hexose molecules are tied together through oxygen and not by a direct attachment of carbon to carbon. The sugar has none of the properties of aldehydes and ketones, and hence we must assume that the carbonyl groups of the glucose and fructose molecules are rendered inactive when they unite to form the disaccharide. The following formula, although not definitely established, is in harmony with these facts: *

* It has been reported that when cane sugar is completely methylated and subsequently hydrolyzed the products are 2, 3, 5, 6-tetramethylglucose and tetramethyl γ-fructose. On the basis of this result the following formula has been proposed:





Cane sugar has been synthesized, but the methods employed furnish no further evidence concerning the structure of the molecule. With lime the sugar forms soluble mono- and di-calcium saccharates, $C_{12}H_{22}O_{11} \cdot CaO \cdot 2H_2O$ and $C_{12}H_{22}O_{11} \cdot 2CaO$, and an insoluble trisaccharate, $C_{12}H_{22}O_{11} \cdot 3CaO \cdot 3H_2O$. These molecular compounds are readily decomposed by dilute acids. Carbon dioxide releases sugar from alkaline solutions of calcium saccharates, calcium carbonate being precipitated.

BEET SUGAR

Sugar obtained from beets, when pure, is identical with pure cane sugar, and the commercial product from either source should contain less than one per cent of impurities. The foreign matter retained by sugar crystals varies in character with the source. It is possible, therefore, to distinguish between crude specimens of cane and beet sugar by identifying the impurities, but impossible to detect any difference between pure samples from the two sources.

In the manufacture of sugar from beets care is exercised to avoid unnecessary rupturing of the cell walls. The beets are not crushed and pressed, as is the practice in extracting the juice of cane; but the sucrose is allowed to diffuse out of the cells of the plant tissue into water, leaving in the extracted pulp large quantities of less diffusable bitter substances that would contaminate the product if the juice were expressed from the ground or crushed material.

The beets are cleaned by scrubbing in warm water, then conveyed to automatic scales, weighed, and transferred to the slicer, a mill provided with rotating blades that cut the beets in long, slender strips called cossettes. These are conveyed to the diffusion battery, which consists of twelve or

more steel tanks (cells of the battery), each having a capacity of two or three tons of cossettes. A stream of hot water enters at the top of one tank, passes down through the pulp, and is forced up through a heating tube to the top of the second cell, and so on. The solution passes from one unit of the battery to another, finally emerging with a sugar content almost equal to that in the tissue fluids of freshly cut cossettes. The process is continuous. Fresh water is delivered to the tank that contains pulp, from which the sugar has been almost completely removed, and as it passes through the battery it encounters, in each succeeding cell, pulp that is richer in sugar until it finally passes through a tank containing cossettes just received from the slicer. There are always two cells of the battery out of the diffusion circuit. From one the waste pulp is being discharged, while the other is being filled with new material. The sugar solution as drawn from the diffusion battery is dark in color. It is clarified by the addition of milk of lime, $Ca(OH)_2$, and subsequent precipitation of the calcium as carbonate by treatment with carbon dioxide. Colloidal substances suspended in the aqueous extract are mechanically carried down with the precipitate and removed from the juice by filtration. Further purification is effected by treating the solution with sulphur dioxide and again filtering. To avoid hydrolysis of the sugar, complete neutralization of the calcium hydroxide by sulphurous acid is carefully avoided.

The clarified juice is evaporated under reduced pressure, until the sugar crystallizes, and the mother liquor is then removed by means of centrifugal filters. The sugar is dried in rotating tubes, five or six feet in diameter and twenty feet long, through which it is made to travel against a counter current of hot air.

Estimation. The sugar content of a solution is estimated by a determination of its optical rotation. Sucrose is strongly dextro-rotatory, $(\alpha)_D = 66.5°$. Optically active proteins are present in the juice obtained from beets, and these have to be removed before the analysis is made. The proteins are precipitated and the solution is rendered optically clear by treatment with lead acetate. To estimate sucrose in the presence of glucose, or any other monose, the optical rotation of the mixture is measured and the solution is then boiled with hydrochloric acid to hydrolyze the disaccharide, and returned to the polarimeter for a second reading. From the change in the angle of rotation caused by substitution of invert sugar for sucrose, the quantity of the latter in the original mixture may be calculated.

MALTOSE

Under the influence of an enzyme known as diastase, which is present in sprouting barley, starch is hydrolyzed to maltose, a disaccharide, $C_{12}H_{22}O_{11} \cdot H_2O$. And maltose is hydrolyzed to glucose by an enzyme, maltase, found in most yeasts. Both of these ferments are present in the fluids of the alimentary canal.

Maltose crystallizes in the form of needles. It forms an osazone with phenylhydrazine and reduces Fehling's solution,

indicating the presence of a carbonyl group. Only one aldehyde group is involved in the union of two glucose molecules when they combine to form maltose. A linkage of this type between monoses is referred to as a monocarbonyl bond. It will be recalled that cane sugar has none of the properties of an aldehyde or ketone. The aldehyde structure of glucose and the ketone structure of fructose are both destroyed in the union between the two hexoses. Such a linkage is called a dicarbonyl bond.

LACTOSE

The only important source of lactose is milk. The fat is separated from milk for the manufacture of butter and the casein is then precipitated by an enzyme, rennet, and is used in making cheese. Lactose or milk sugar remains in the whey, from which it may be obtained by evaporating the latter to a small volume. The crystals of lactose are hard and they dissolve slowly. The solution is dextro-rotatory. Lactose is not as sweet as cane sugar. It forms an osazone and reduces ammoniacal silver solutions. On hydrolysis lactose yields *d*-glucose and *d*-galactose. It may be oxidized by bromine water to lactobionic acid, and this on hydrolysis yields *d*-galactose and *d*-gluconic acid. The unchanged aldehyde group is, therefore, in the glucose half of the molecule.

Lactose is used in the preparation of mucic acid, $COOH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHOH \cdot COOH$, which is derived from the galactose half of the molecule by oxidation with nitric acid.

Lactose is converted into lactic acid, $CH_3 \cdot CHOH \cdot COOH$, by *Bacterium lactis acidi* or by *Streptococcus lacticus*. A few other microörganisms accomplish the same thing. This transformation, known as lactic fermentation, is the cause of the souring of milk.

POLYSACCHARIDES

Starch, inulin, glycogen, and cellulose are typical polysaccharides. They are amorphous carbohydrates of high molecular weight, and they are almost tasteless. On hydrolysis they yield monoses. Those mentioned above yield hexoses, but some polysaccharides yield pentoses. Although many members of this group are fairly soluble in water, they do not

produce appreciable lowerings in the vapor pressure of the solvent. It is impossible, therefore, to determine their molecular weights; but the values must be very high. A polysaccharide is made up of n monose molecules less $n - 1$ molecules of water; and if n is large, the composition of the compound approaches the value expressed by the empirical formula, $(C_6H_{10}O_5)_n$.

STARCH

Starch, $(C_6H_{10}O_5)_n$, is present in large quantities in all plants. It is especially abundant in potatoes and other tubers, and in wheat, corn, rice, and other cereals. It occurs in the form of granules, and each source of starch yields granules of characteristic form. By microscopic examination of starch it is often possible to determine its origin.

When heated, starch is partly converted into polysaccharides of lower molecular weight, known as dextrins. When boiled with dilute acids, it is hydrolyzed to glucose. The enzyme, diastase, acts upon a suspension of starch in water, hydrolyzing the starch to maltose and isomaltose. In cold water starch is insoluble. In hot water the granules swell, forming a paste. A highly dispersed suspension of starch particles (colloidal solution) is obtained in boiling water. Starch paste is used as an indicator for free iodine. A deep blue color is produced when starch absorbs iodine. In the process of digestion starch is converted into glucose.

Formaldehyde has been condensed to acrose, a sugar isomeric with glucose, and since starch is a polymer of glucose, it has been suggested that starch is formed in plant tissue by a condensation of this type. Carbon dioxide taken into the plant through the leaves, and water entering by way of the roots, furnish the components from which formaldehyde may be made:

$$CO_2 + H_2O \longrightarrow HCHO + O_2.$$

Many molecules of formaldehyde condensing may yield the carbohydrate starch. In the laboratory six molecules only have been made to unite:

$$\begin{aligned} &HCHO + HCHO + HCHO + HCHO + HCHO + HCHO \\ &\longrightarrow \underset{\text{Acrose}}{CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHO} \end{aligned}$$

The theory that formaldehyde is formed in the plant as the starting point in the synthesis of starches and sugars was first advanced by Baeyer.* The theory has been supported by many investigators, including Usher and Priestly,† Baly,‡ Moore and Webster,§ and others. They claim that the production of formaldehyde from carbon dioxide and water is a photochemical process which occurs under the influence of sunlight in the presence of chlorophyl, and that similar results can be obtained, *in vitro*, by exposing an aqueous solution of carbon dioxide to ultraviolet radiation. On the other hand, Spoehr‖ claims that formaldehyde is not produced from water and carbon dioxide alone under the influence of ultraviolet light.

GLYCOGEN

Glycogen, $(C_6H_{10}O_5)_n$, a white, amorphous substance, constitutes the reserve supply of carbohydrate in the animal organism. It occurs primarily in the liver, but is present also in all muscular tissue. The energy change involved in the oxidation of carbohydrates contributes largely to the maintenance of the body temperature, and to the development of muscular activity. Glycogen is hydrolyzed to glucose as rapidly as the latter disappears from the blood. After a meal rich in carbohydrates, glucose reaches the blood stream more rapidly than it is required in the oxidation processes of the tissues; and by a reversal of the hydrolysis process it is converted into glycogen, which is stored in the liver and elsewhere.

Glycogen acquires a red color when treated with iodine.

INULIN

Inulin, $(C_6H_{10}O_5)_n$, resembles starch in many respects, but differs from it in being fairly soluble in water and in producing no color with iodine. Inulin is found in many plants. Artichokes, dahlia tubers, and chicory roots are especially productive of this polysaccharide. It is hydrolyzed very rapidly when boiled with a dilute acid and yields fructose only.

* Baeyer, *Ber.*, **3**, 73 (1870).

† Usher and Priestly, *Proc. Roy. Soc.*, **84**, B, 101 (1911).

‡ Baly, Helibron, and Barker, *Trans. Chem. Soc.*, **119**, 1025 (1921).

§ Moore and Webster, *Proc. Roy. Soc.*, **90**, B, 168 (1918).

‖ H. A. Spoehr, *J. Am. Chem. Soc.*, **45**, 1184 (1923). Porter and Ramsperger, *J. Am. Chem. Soc.*, **47**, 79 (1925).

CELLULOSE

Cellulose constitutes the principal building material of the cell walls in plants. It is associated with lignin, a compound of unknown structure found in the bark and wood of all trees.

Cotton, linen, and paper are composed of cellulose. Ashless filter paper is pure cellulose. Cellulose from most sources yields glucose only, when hydrolyzed; but that derived from coffee-beans and from a few other sources yields *d*-mannose. Cellulose is of great technical importance. The uses of cotton, linen, and paper are almost numberless; and in addition to its uses in an unaltered state, it is the source of such preparations as nitrocellulose, guncotton, collodion, and artificial silk. For descriptions of these products the books and journals devoted to industrial chemistry should be consulted.

ENZYMES

A chemical substance derived from a living cell and capable of changing the rate of a chemical reaction by contact with the reagents is called an enzyme. The enzyme itself is not changed nor destroyed in the reaction which it accelerates or retards. It is an organic compound which acts as a catalyst. In displaying more or less specificity of action enzymes differ, in degree at least, from inorganic catalysts. For example, an enzyme that causes the fermentation of *d*-glucose will not produce a similar change in the isomeric *l*-glucose. This fact led Fischer to assume that there must be a definite relationship between the molecular structure of the enzyme and that of the substance upon which it acts. He made the idea more definite by comparing the substrate to a lock and the enzyme that acts upon it to a key that has the proper configuration to turn the lock. Bayliss thinks this analogy has been overworked and claims that not all enzymes are specific in their catalytic effects.

Enzymes act only at moderate temperatures. Below zero they are inactive, but the activity is restored when the solution is warmed. They are permanently destroyed by temperatures approaching 100° C.

It is said that a catalyst cannot initiate a reaction, its function being limited to that of changing the rate of a process already going on. There are apparent exceptions to the rule. A dilute solution of milk sugar remains unchanged for years in the absence of catalysts, but is hydrolyzed within a few hours in the presence of an enzyme, lactase. Hydrogen and oxygen constitute a stable and unreactive mixture at low temperatures, but in the presence of spongy platinum they combine rapidly. Those who insist that a catalyst cannot initiate a reaction maintain that in these and similar cases the reactions proceed in the absence of catalysts, but at immeasurably slow rates. There is, of course, no way to refute the argument.

One of the first cases of enzyme action to be carefully studied was that of the production of alcohol from sugar, through fermentation induced by yeast. Pasteur believed that fermen-

tation was a result of physiological processes in the living yeast cell. He assumed that sugar was a food for the living organism and alcohol a product of carbohydrate metabolism within the cell. The production of alcohol was due, therefore, to certain biological functions of living microörganisms. This theory of fermentation was accepted until Buchner's classical experiment (1897) indicated a different cause for the process. Buchner triturated yeast with sand until all cell walls were ruptured. He extracted the mass with water and forced the solution through an unglazed porcelain filter. The filtrate was an optically clear solution containing no living cells. Incubation under optimum conditions of temperature and nutriment produced no sign of life. Yet this sterile solution of substances extracted from the living cells was found to be as potent as the yeast plant itself in causing alcoholic fermentation of glucose. The decomposition of glucose into alcohol and carbon dioxide is accomplished under the influence of an unorganized ferment — a chemical compound — derived from the yeast cells. Buchner called this substance zymase. It is a typical enzyme. Yeast produces another enzyme, invertase, which catalyzes the hydrolysis of cane sugar. Zymase operates only on the invert sugar (glucose and fructose).

If it were not removed from the field of action, a very small quantity of an enzyme would be sufficient to change an unlimited amount of the substrate. Loss of the catalyst may be due to side reactions in which it is directly involved as a reagent, or it may be mechanically carried out of the mixture by adsorption on the surfaces of products formed in the main reaction. Invertase in a solution of cane sugar remains active until more than 200,000 times its own weight of sucrose has been hydrolyzed, and rennet is said to precipitate from milk as much as 400,000 times its weight of casein.

Practically all of the processes catalyzed by enzymes are reversible reactions and Bayliss* has presented evidence in support of the claim that any enzyme that catalyzes the decomposition of a compound in a reversible process likewise catalyzes its synthesis from the decomposition products. Gay and Robertson,† on the other hand, have cited cases which

* Bayliss: The Nature of Enzyme Action (1919).

† Gay and Robertson: "A comparison of paranuclein, split from casein, with a synthetic paranuclein based on immunity reactions." *J. Biol. Chem.*, **12**: 233 (1912).

seem to indicate that the hydrolysis of a protein may be accelerated by means of an enzyme which lacks the power to synthesize the substance from the hydrolysis products. If this be true we must conclude that such an enzyme is not a true catalyst or that the reaction is not reversible. A true catalyst influences the rates of both processes involved in a reversible reaction and does not affect the final state of equilibrium.

In practically all of the examples of enzyme action on carbohydrates and proteins, in vitro, equilibrium is attained only when the substance has been almost completely hydrolyzed. On the other hand, synthetic processes occur rapidly and quite completely under the influence of enzymes in the tissues of the animal organism. It is a matter of some importance to determine definitely whether both types of action are accomplished by the same enzyme, the course being determined by the varying activities of the components in different environments, or if hydrolysis and synthesis represent specific results of two different types of enzymes.

There are obstacles in the way of securing unambiguous results in the study of enzyme action. For example, we cannot be sure that any one has succeeded, as yet, in isolating a chemically pure specimen of an enzyme. The ordinary criteria of purity cannot be applied to enzymes. They do not crystallize and they decompose below their melting points. Their molecular weights are unknown, for like other colloids they produce very slight depressions of freezing points and very low osmotic pressures, these values being very little greater than the effects that might be attributed to impurities in the samples. Pepsin and trypsin are typical protein-splitting enzymes of the alimentary tract. They respond to the ordinary tests for proteins, but the observed protein reactions may be due to adsorbed foreign substances. Similarly, invertase, an enzyme that acts upon sucrose, responds to tests for carbohydrates; but that does not justify the conclusion that pure invertase is itself a carbohydrate. Attempts to purify an enzyme often result in reducing its activity as a catalyst. This may be due to removal of a co-enzyme — a substance that works with the enzyme or establishes optimum conditions for its active operation. Pepsin, for instance, is inactive in the absence of hydrochloric acid; and the fat-splitting enzyme, lipase, of the liver is active only in the presence of bile.

Enzymes are obtained from many sources. Some are found in solution in the body fluids; as, for example, ptyalin in saliva, pepsin in gastric juice, and trypsin in pancreatic juice. Others have to be extracted with water, or any suitable solvent from ground cells. Invertase and zymase are obtained from yeast in this way, and erepsin is extracted from the mucous lining of the intestine.

A few of the best-known enzymes are listed below with a tabulation of sources, the substrates upon which they act, and the products of the reactions.

Enzymes	Sources	Substrates	Products
Ptyalin	Saliva	Starch, dextrin	Maltose
Amylopsin	Pancreatic juice	Starch, dextrin	Maltose
Glycogenase	Liver, muscles	Glycogen	Dextrin, maltose, glucose
Inulase	Fungi	Inulin	Fructose
Lactase	Intestinal mucosa	Lactose	Glucose and galactose
Maltase	Blood serum, liver, saliva, pancreas, lymph	Maltose	Glucose
Invertase	Intestinal mucosa, yeast	Sucrose, glucosides	Glucose, fructose
Zymase	Yeast	Sugars	Alcohol and carbon dioxide
Adenase	Animal tissues	Adenine	Hypoxanthine
Emulsin	Plant tissues	Glucosides	Monoses
Steapsin	Pancreatic juice	Fats	Glycerol and fatty acids
Erepsin	Succus entericus	Polypeptides, peptones	Amino acids
Rennin	Gastric juice, pancreas	Casein	Paracasein
Thrombin	Blood	Fibrinogen	Fibrin
Pepsin	Gastric juice	Proteins	Peptones, polypeptides
Trypsin	Pancreatic juice	Proteins	Peptones, polypeptides, amino acids

THE PURINES

The important derivatives of purine are uric acid, caffeine, theobromine, theophylline, xanthine, guanine, and adenine. These names were applied to the compounds before their chemical structures and genetic relationships had been established. The names, however, are so well known and so commonly employed that it will take a long time to supplant them by a systematic nomenclature.

An acquaintance with the products obtained when purine bodies are oxidized makes it possible to assign to each of them a definite structure.

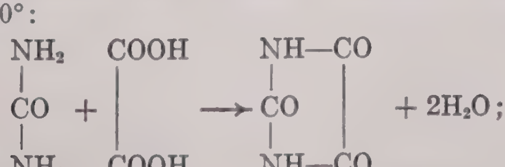
The ureids. Urea is an amide of carbonic acid. Retaining to some extent the character of ammonia, it reacts with acids, forming secondary amides. Thus, for example, it combines with one molecule of acetic acid, forming acetylurea, and with two molecules, forming symmetrical diacetylurea:

$$CO\begin{matrix} \diagup NH_2 \\ \diagdown NH_2 \end{matrix} + CH_3 \cdot COOH \longrightarrow CO\begin{matrix} \diagup NH \cdot COCH_3 \\ \diagdown NH_2 \end{matrix} + H_2O,$$

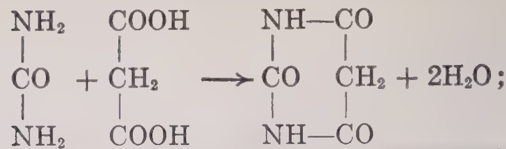
$$CO\begin{matrix} \diagup NH_2 \\ \diagdown NH_2 \end{matrix} + 2CH_3 \cdot COOH \longrightarrow CO\begin{matrix} \diagup NH \cdot COCH_3 \\ \diagdown NH \cdot COCH_3 \end{matrix} + 2H_2O.$$

Acetylurea crystallizes in long, silky needles, melting at 214°. Diacetylurea melts at 153°. When boiled with acids, they both decompose into acetic acid, carbon dioxide, and ammonia.

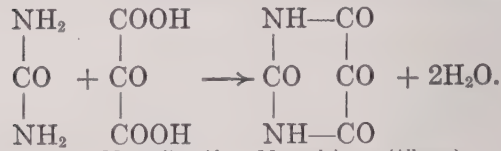
Ureids are formed also by the union of urea with dibasic acids such as oxalic and malonic. The reaction is usually carried out by dehydrating a mixture of the acid and urea with phosphorus oxychloride, $POCl_3$, at temperatures ranging from 100° to 200°:



Urea Oxalic acid Oxalyl urea (Parabanic acid)

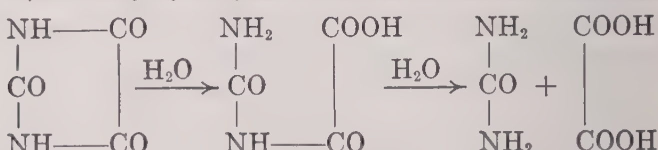


Urea Malonic acid Malonyl urea (Barbituric acid)



Urea Mesoxalic acid Mesoxalyl urea (Alloxan)

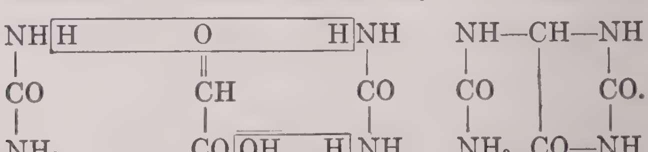
These cyclic compounds are crystalline solids. They are all readily decomposed by boiling with alkali, the hydrolysis occurring in two stages. Oxalyl urea, commonly called parabanic acid, reacts with one molecule of water to yield oxaluric acid, but in complete hydrolysis two molecules of water are used, the products being oxalic acid and urea. The latter, being an amide, is finally hydrolyzed to carbon dioxide and ammonia:



Parabanic acid Oxaluric acid Urea Oxalic

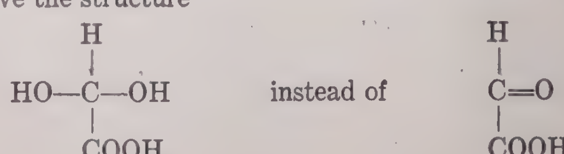
Similar reactions occur with all ureids.

Two molecules of urea combine with one of glyoxalic acid to form allantoin. The condensation may be written as follows:



Glyoxalyl urea (Allantoin)

Glyoxalic acid is always associated with one molecule of water, and although it has all the properties of an aldehyde acid, it may have the structure

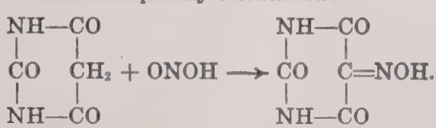


It is one of the very few compounds in which two hydroxyl groups seem to be held by the same carbon atom. The formation of allantoin is cited as evidence for the dihydroxy formula for glyoxalic acid. However, there is nothing unusual about the removal of an aldehyde oxygen atom as indicated in the above equation.

Allantoin is a tasteless, odorless, crystalline substance, which melts and decomposes at 231°. It forms insoluble salts of lead, silver, copper, and mercury. It is soluble in water, and in alcohol, and is hydrolyzed by hot acids or alkalies to carbon dioxide, ammonia, oxalic acid, and acetic acid.

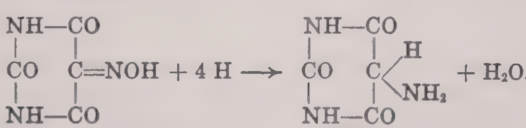
The hydrogen atoms in the malonic acid residue of malonyl urea are replaceable by metals or by halogens, as they are in malonic ester. Thus, by the action of sodium and subsequent treatment with an alkyl halide, any mono- or di-alkyl derivative of barbituric acid may be prepared.

Malonyl urea reacts with nitrous acid, yielding violuric acid, and hydroxylamine acts upon mesoxalyl urea to form the same compound. The structure of violuric acid is consequently established:



Malonyl urea Violuric Acid

Violuric acid is a colorless, crystalline solid. Its esters are colorless also; but it forms yellow, red, and blue salts. The structures of these salts have not been determined with certainty. Reduction of violuric acid leads to the formation of uramil:



Uramil

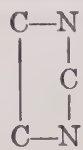
URIC ACID

Uric acid occurs in small quantities in the blood and in normal urine. It is present in large amounts in guano (18 per cent to 25 per cent), and is the chief component of the excrement of serpents. It is crystalline, odorless, and tasteless, very slightly soluble in water (1 : 10,000), and insoluble in alcohol and ether. Even the alkali metal salts of uric acid are only sparingly soluble. The monosodium salt dissolves in 1100 times its

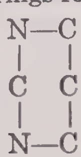
weight of water at 15°; the corresponding lithium salt dissolves in 370 parts of water. The disodium salt is more soluble, (1:60).

The history of the researches that led to the proof of the structure of uric acid is fascinating and instructive. It reveals the gradual growth of the structure theory, as one contribution after another shed new light on the problem. Only an outline of the problem can be given here. The first serious attempt to determine the chemical nature of uric acid was made by Baeyer in 1863. The accepted formula was proposed by Medicus in 1875, and its validity was proved by Fischer in 1883.

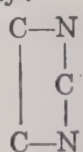
When oxidized by potassium permanganate in alkaline solution, uric acid yields allantoin. It, therefore, contains two urea residues and the ring structure found in allantoin:



When oxidized with nitric acid, uric acid yields alloxan and parabanic acid. It, therefore, possesses a structure that includes the rings found in these ureids, namely:

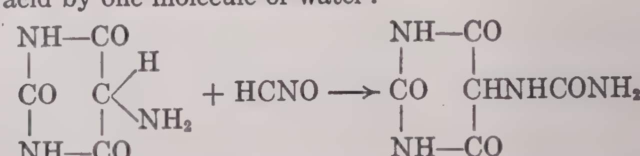


and



From the results obtained by analyses and molecular-weight determinations, its molecular formula is shown to be $C_5H_4N_4O_3$.

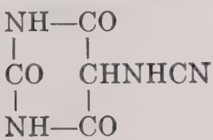
By condensing cyanic acid with uramil, Baeyer synthesized a compound which he called pseudo-uric acid. It differs from uric acid by one molecule of water:



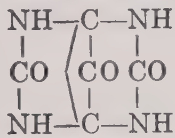
He tried in vain to dehydrate this compound in such a way as to leave uric acid. Fischer completed Baeyer's task by dehy-

drating pseudo-uric acid through the agency of hot hydrochloric acid. Uric acid was thus produced.

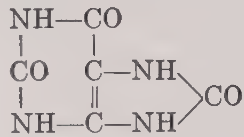
On the basis of these facts, Baeyer, Fittig, and Medicus proposed the following structures for the uric acid molecule.



Baeyer



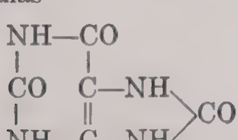
Fittig



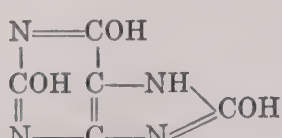
Medicus

Fischer proved the presence of four imide groups in uric acid by preparing a tetramethyl derivative, from which all of the nitrogen in the compound could be obtained, by saponification, in the form of methyl amine. This evidence was completely in harmony with the formulas proposed by Medicus and Fittig, but ruled out the Baeyer structure. Hill, at Harvard, made the next advance by preparing two different monomethyl derivatives in each of which the methyl group was attached to nitrogen. The symmetrical formula of Fittig, therefore, had to be rejected. Finally, Fischer confirmed the Medicus formula by showing that on oxidation, one of Hill's monomethyl derivatives yields alloxan and methyl-urea, whereas the other, under similar treatment, yields methyl-alloxan and urea. In other words, only one of the two imide (NH) groups in which the methyl radical had been substituted was in the alloxan ring. The structure has been confirmed also by at least three different methods for producing the compound synthetically.

In many of its reactions uric acid acts as if its oxygen atoms were in hydroxyl groups. Phosphorus trichloride, for example, acts upon uric acid, forming trichlorpurine. In the process three oxygen and three hydrogen atoms are replaced by three chlorine atoms. In some other reactions uric acid behaves like a ketone. It is a phenomenon similar to that displayed by the oximes and acetoacetic ester. It is a case of keto-enol tautomerism, and the two structures of uric acid correspond to the formulas



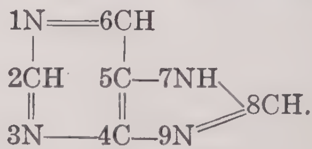
Keto form



Enol form

PURINE

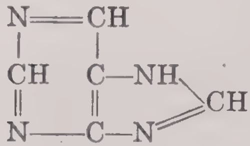
A colorless, crystalline compound composed of carbon, hydrogen, and nitrogen only, and having the same condensed carbon and nitrogen rings as found in uric acid is known as purine. Its structure was written and the name applied to it fourteen years before the compound was known to exist. It was, therefore, at first a purely hypothetical substance representing what might be expected to form, if uric acid could be reduced until it contained only the three elements mentioned, without changing the ring structure. Uric acid and all other compounds having the same carbon-nitrogen skeleton are regarded as purine derivatives and named in accordance with the positions occupied by substituting groups. The positions of the elements in the purine rings are numbered as follows:



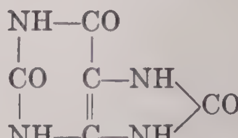
Purine

Purine is a very weak base. It melts at 217° and dissolves readily in water. All of its oxy-derivatives display a keto-enol tautomerism corresponding to that of uric acid.

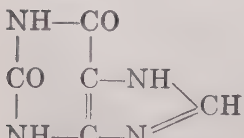
The close relationship between the compounds mentioned in the first paragraph of this chapter is made apparent by a comparison of their structural formulas. The systematic names and the common names are both given, the latter in parenthesis:



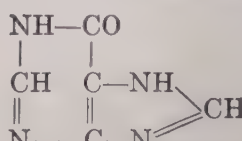
Purine



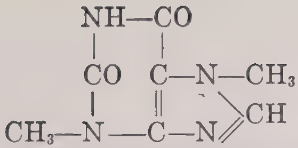
2, 6, 8-Trioxypurine (Uric acid)



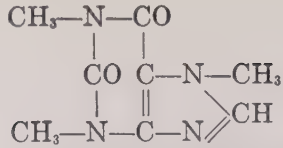
2, 6-Dioxypurine (Xanthine)



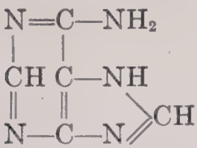
6-Oxypurine (Hypoxanthine)



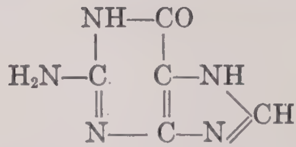
3, 7-Dimethyl-2, 6-dioxypurine (Theobromine)



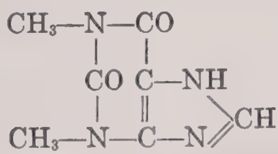
1, 3, 7-Trimethyl-2, 6-dioxypurine (Caffeine)



6-Aminopurine (Adenine)



2-Amino-6-oxypurine (Guanine)



1, 3-Dimethyl-2, 6-dioxypurine (Theophylline)

Caffeine crystallizes from water in white needles, having a silky luster and a bitter taste. It sublimes under atmospheric pressure at 178°, and melts in a sealed tube at 235°. Caffeine occurs in coffee (0.5 per cent to 1.5 per cent) and in tea (2 per cent to 3.5 per cent). Its physiological action is of some importance. It acts upon (1) the central nervous system, (2) upon the kidneys, and (3) upon the heart. It is a cerebral stimulant. It overcomes drowsiness, relieves fatigue, and brightens the intellectual faculties. The system, however, acquires tolerance for the drug and these effects are not realized by one accustomed to its use. It is a heart stimulant. Intravenously injected it quickens the heart action and temporarily produces a stronger pulse, comparable to the effects of strychnine. Upon the kidneys it acts as a diuretic, and on this account its use has been advocated in the treatment of various types of œdema. In addition to these chief characteristics one other effect should be mentioned, which, however, is not general but depends largely upon the idiosyncrasies of individuals, namely, its influence upon digestion. Many suffer from indigestion if caffeine is used in large amounts.

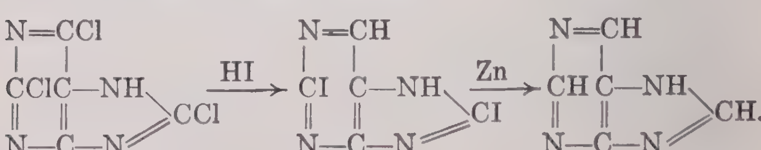
Theobromine is found in chocolate (1 per cent to 2 per cent). It is a colorless, crystalline body which sublimes at 290°. Like

caffeine it is a nerve stimulant and a diuretic. It is only slightly soluble in water and in alcohol but dissolves readily in ether. Theobromine, caffeine, and other purines are partly oxidized in passing through the body and are excreted chiefly in the form of uric acid.

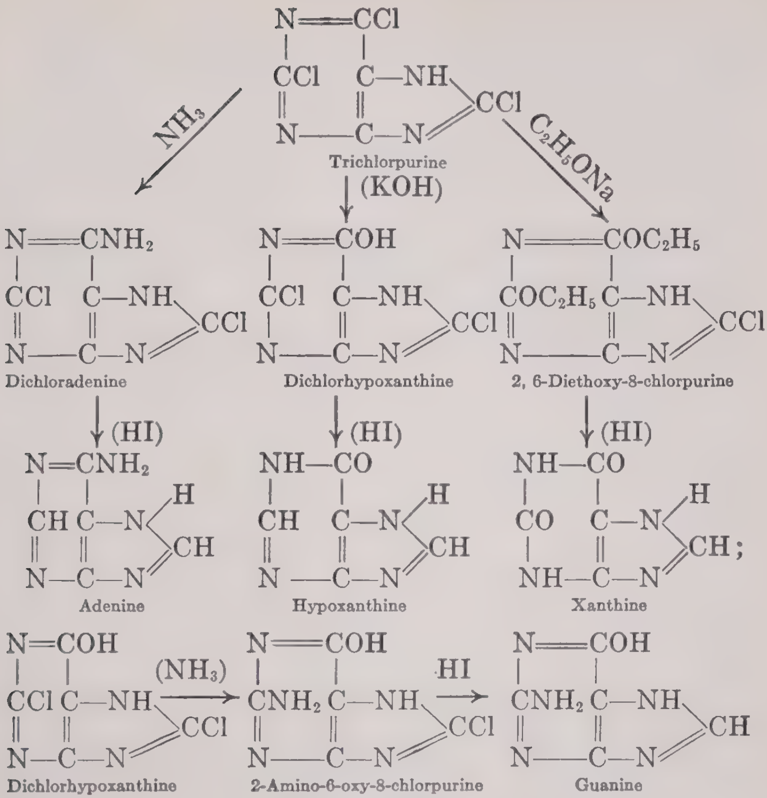
Adenine is obtained as a hydrolysis product of nucleo-proteins of both plant and animal origin, and may be obtained in crystalline form from an aqueous extract of tea leaves. It decomposes at 360°.

Guanine occurs with adenine in plant and animal tissues and especially in nucleic acid. It is practically insoluble in water and in alcohol, but dissolves in basic solutions. Guanine and adenine are the only amino purines found in nature.

Trichlorpurine is prepared by treating uric acid with phosphorus oxychloride; and from this derivative most of the purine bases may be made by direct processes of substitution. The control of these substitutions is rendered possible by the fact that the chlorine in position 6 is far more reactive than either of the others, and the halogen atom in position 2 is more reactive than the one in position 8. Thus, when 2, 6, 8-trichlorpurine is warmed with hydriodic acid, only chlorine 6 is replaced by hydrogen. Chlorine atoms 2 and 8 are, at the same time, replaced by iodine. The di-iodopurine may be completely reduced, by heating with zinc dust and water, and in this way purine was synthesized:

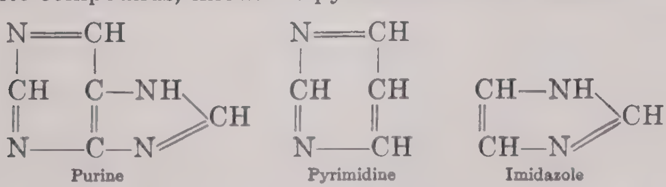


Ammonia acts upon trichlorpurine, replacing the chlorine at position 6 by NH_2. Potassium hydroxide replaces the same chlorine by hydroxyl. Sodium alcoholate replaces chlorine atoms 2 and 6 by alkoxyl groups; and in any of these derivatives the remaining chlorine may be replaced by hydrogen through reduction with hydriodic acid and zinc. The principal reactions involved in the conversion of trichlorpurine into other derivatives of purine are summarized in the following table:



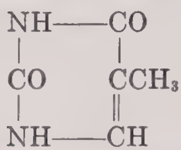
THE PYRIMIDINES

The purine molecule contains a six-membered ring and a five-membered ring. The two are merged so that two of the carbon atoms belong to both rings. The separate rings, with hydrogen enough to satisfy the carbon valences, represent two definite compounds, known as pyrimidine and imidazole:

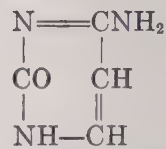


The atoms of the pyrimidine ring are numbered just as they are in purine, and derivatives of this cyclic structure are named

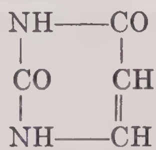
as substituted pyrimidines. As a result of the exhaustive researches of Treat B. Johnson, the reactions of the pyrimidines and methods for synthesizing them are well known. Some of these derivatives are important components of every living cell. The nucleoproteins, for example, are composed of simple proteins, combined with a substance of unknown structure called nucleic acid; and nucleic acid when hydrolyzed yields phosphoric acid, carbohydrates, purines, and pyrimidines. Among the more important members of the last class are thymine, cystosine, and uracil:



5-Methyl-2, 6-dioxypyrimidine (Thymine)

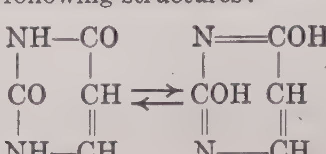


6-Amino-2-oxypyrimidine (Cystosine)



2, 6-Dioxypyrimidine (Uracil)

They are not very soluble in water. They decompose at their melting points, thymine 321°, cystosine 324°, and uracil 338°. On treatment with nitrous acid cystosine is converted into uracil. It is the usual replacement of an amino group by hydroxyl. In the same way adenine is converted into hypoxanthine and guanine into xanthine. Uracil and other oxypyrimidines, and the oxypurines as well, exist in two forms corresponding to keto and enol structures. In solution an equilibrium is established between the two forms. If a reagent is used which reacts with a carbonyl oxygen, any one of these tautomeric compounds will behave as if it were a pure ketone. With a reagent which acts on a hydroxyl group the same compound responds with equal ease in the enolic form. Uracil in solution has the following structures:



THE PROTEINS

A group of complex compounds known as proteins constitute the major part of the solid matter in the skin, muscle, nerve, blood, hair, and nail of the animal organism. They occur also as essential constituents of every plant. They are, therefore, compounds of the utmost importance to all forms of life, and especially to animal life, where their rôle corresponds to that of the carbohydrates in plants. No substitution can be made for proteins in the diet. They are absolutely necessary for the continuance of life.

Formulas have been assigned to about sixty proteins, and there are probably hundreds of stereoisomeric forms in nature, corresponding to each empirical formula. The molecular weights of proteins have not been determined with precision, and we are hardly justified in assigning definite molecular formulas even to the few crystalline proteins that represent the purest types known. The ordinary criteria of purity, for example, sharp melting point, melting point unchanged by recrystallization, constant boiling point, and so on, cannot be applied; for proteins decompose before they melt. The best that can be done is to secure a homogeneous sample that can be recrystallized or reprecipitated without change in composition.

Many proteins are readily soluble in water, but the depression of the freezing point and elevation of the boiling point due to the dissolved substances never exceed a few hundredths of a degree, and the probable experimental error amounts to a large per cent of the total observed change. Osmotic pressure determinations are even less satisfactory.

We have chemical means of fixing the minimum values of the molecular weights of some proteins; and these values in some cases agree with the best estimate that can be made on the basis of measurements of the physical properties of their solutions. Hæmoglobin contains 0.4 per cent of iron. In one molecule of hæmoglobin there cannot be less than one atomic weight of iron. From the proportion, $0.4 : 100 = 56 : M$, the minimum

value for the molecular weight is 14,000. It contains sulphur also (0.38 per cent). Cystine has been identified as one of the products formed when hæmoglobin is hydrolyzed and cystine contains two atoms of sulphur. If all of the hæmoglobin sulphur is in cystine groups, there must be at least two atoms of sulphur in the hæmoglobin molecule. From the proportion, $0.38 : 100 = 64 : M$, we have for the minimum value 16,840.

The quantity of oxygen that combines with hæmoglobin under various pressures has been measured.* Assuming that one molecule of oxygen combines with one molecule of the protein, the molecular weight of the latter must be a little more than 16,000. Practically the same value is indicated by the osmotic pressure measurements of Hufner and Gausser†. It seems reasonably certain, therefore, that the molecular weight of hæmoglobin is approximately 16,000. Still, we have no positive assurance that a chemically pure specimen of hæmoglobin has ever been prepared, and it must not be forgotten that slight but constant contamination with foreign matter could vitiate measurements of all types and lead to false conclusions.

Though differing widely in many chemical and physical properties, the proteins are remarkably similar in composition. Most of them are composed of only half a dozen elements, and the relative proportions of these few elements vary between narrow limits. The minimum and maximum values are as follows:

	Per Cent
Carbon	50 — 55
Oxygen	19 — 25
Nitrogen	15 — 19
Hydrogen	5 — 8
Sulphur	0 — 5
Phosphorus	0 — 1
Other elements	0 — 1

It was realized more than a century ago that the only hope of securing an insight into the nature of the proteins was by decomposition of the complex molecule and identification of the simpler groups thus produced. The early researches were directed toward the decomposition products obtained by fusion with alkali or by oxidation with nitric acid or with potassium permanganate. No important discovery was made on the basis of these investigations.

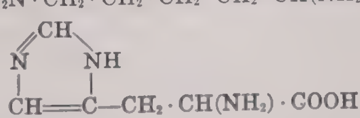
* Wertheimer, *Biochem. Zeit.*, **106**, 12 (1920).

† Hufner and Gausser, *Arch. anat. Physiol.*, **209** (1907).

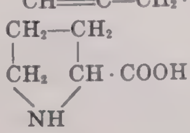
In 1820 Braconnot hydrolyzed a protein by boiling with dilute sulphuric acid and identified glycine (aminoacetic acid) as one of the hydrolysis products. This was the first important step towards the solution of the problem. Hydrolysis is accomplished in a variety of ways: (1) boiling in acid solution; (2) boiling in alkaline solution; (3) action of superheated steam; (4) the action of enzymes. All of these methods were applied to all of the available proteins during the last half of the nineteenth century; and one by one the various units were isolated and identified. Seventeen amino acids have been definitely identified as constituents of the simple proteins. Some proteins contain all of them. In each of these acids an amino group (NH_2) is attached to an α-carbon atom; that is, a carbon atom adjacent to the carboxyl group.

Amino Acids

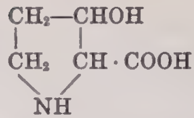
1. *Glycine:* $CH_2 \cdot (NH_2) \cdot COOH$
2. *Alanine:* $CH_3 \cdot CH(NH_2) \cdot COOH$
3. *Valine:* $\begin{matrix} CH_3 \\ CH_3 \end{matrix} \!\!> CH \cdot CH(NH_2) \cdot COOH$
4. *Leucine:* $\begin{matrix} CH_3 \\ CH_3 \end{matrix} \!\!> CH \cdot CH_2 \cdot CH(NH_2) \cdot COOH$
5. *Isoleucine:* $\begin{matrix} CH_3 \\ C_2H_5 \end{matrix} \!\!> CH \cdot CH(NH_2) \cdot COOH$
6. *Phenylalanine:* $C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$
7. *Tyrosine:* $HO \cdot C_6H_4 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$
8. *Serine:* $CH_2(OH) \cdot CH(NH_2) \cdot COOH$
9. *Cystine* $HOOC \cdot CH(NH_2) \cdot CH_2 \cdot S{-}S \cdot CH_2 \cdot CH(NH_2) \cdot COOH$
10. *Aspartic acid:* $HOOC \cdot CH_2 \cdot CH(NH_2) \cdot COOH$
11. *Glutamic acid:* $HOOC \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$
12. *Arginine:* $HN{=}C \begin{matrix} \diagup NH_2 \\ \diagdown NH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH \end{matrix}$
13. *Lysine:* $H_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$
14. *Histidine:*



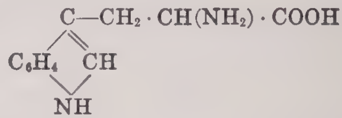
15. *Proline:*



16. *Oxyproline:*



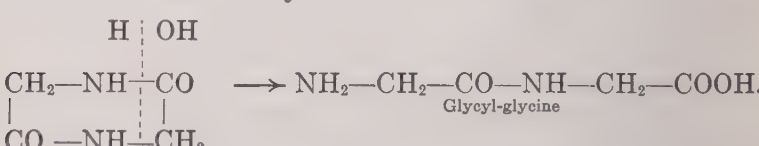
17. *Tryptophane:*



Synthesis of Polypeptides

When amino acids are heated with dehydrating agents, ring compounds are produced by the elimination of water from the amino group of one molecule and the carboxyl group of another. These products belong to the class of compounds known as diketopiperazines. Taking glycine as the simplest example, the formation of the dehydration product is represented as follows:

When warmed with dilute sodium hydroxide or concentrated hydrochloric acid, this product is partly hydrolyzed. One molecule of water is added and the bond between carbon and nitrogen in one of the —CO—NH— groups is broken. The ring structure is thus destroyed.



Glycyl-glycine consists of two amino acid molecules less one molecule of water. The acid residues are linked together through the amino group of one and the carboxyl group of the other. It is a dipeptid. A similar chain consisting of three amino acids (less two mols of water) is a tripeptid. In general, a molecule formed by the elimination of n-1 molecules of water from n molecules of amino acids is a polypeptid. The simple proteins are polypeptids of high molecular weight.

Since glycyl-glycine is itself an amino acid it might be expected to yield an anhydride which, by partial hydrolysis, could be converted into a tetrapeptid, or it might form a mixed

anhydride with a single molecule of any amino acid and give rise to a tripeptid. Attempts to build up polypeptids by this method have failed. Dipeptids are easily made; tripeptids are formed in a few instances, but the limits are soon reached and the hope of synthesizing proteins in this manner has been abandoned. A better method, based upon reactions of halogen derivatives of amino acids, was developed by Fischer. Chlorine and bromine act upon the saturated aliphatic acids, replacing hydrogen by halogen. With practical uniformity the substitution occurs on the α-carbon atom. Propionic acid, for example, yields α-chlor-propionic, $CH_3 \cdot CHCl \cdot COOH$. The corresponding acid chlorides are formed by the action of phosphorus trichloride on the chlor-acids. The chlor-acid chlorides thus produced react energetically with free amino acids, eliminating hydrochloric acid:

$$\underset{\text{Chlorpropionyl chloride}}{CH_3 \cdot CHCl \cdot COCl} + \underset{\text{Tyrosine}}{C_6H_4(OH)CH_2 \cdot CHNH_2 \cdot COOH}$$

$$\longrightarrow \begin{array}{l} CH_3 \cdot CHCl \cdot CO \cdot NH \cdot CH \cdot COOH \\ \qquad\qquad\qquad\qquad\quad\;\; | \\ \qquad\qquad\qquad\qquad\quad CH_2 \cdot C_6H_4 \cdot OH \end{array}$$

The remaining chlorine atom may be replaced by an amino group through the agency of ammonia, and a dipeptid is formed:

$$\begin{array}{l} CH_3 \cdot CHNH_2 \cdot CO \cdot NH \cdot CH \cdot COOH \\ \qquad\qquad\qquad\qquad\quad\;\; | \\ \qquad\qquad\qquad\qquad\quad CH_2 \cdot C_6H_4 \cdot OH \end{array}$$

Alanyl-tyrosine

The dipeptid acts like a free amino acid on other acid chlorides:

$$\underset{\text{Alanyl-tyrosine}}{\begin{array}{l} CH_3 \cdot CHNH_2 \cdot CO \cdot NH \cdot CH \cdot COOH \\ \qquad\qquad\qquad\qquad\quad\;\; | \\ \qquad\qquad\qquad\qquad\quad CH_2 \cdot C_6H_4 \cdot OH \end{array}} + \underset{\text{Chloracetyl chloride}}{CH_2Cl \cdot COCl}$$

$$\longrightarrow \begin{array}{l} CH_2Cl \cdot CO \cdot NH \cdot CH \cdot CO \cdot NH \cdot CH \cdot COOH \\ \qquad\qquad\qquad\quad\;\; | \qquad\qquad\qquad\;\; | \\ \qquad\qquad\qquad\quad CH_3 \qquad\qquad\quad CH_2 \cdot C_6H_4 \cdot OH \end{array}$$

On treatment with ammonia this yields a tripeptid:

$$\begin{array}{l} CH_2NH_2 \cdot CO \cdot NH \cdot CH \cdot CO \cdot NH \cdot CH \cdot COOH \\ \qquad\qquad\qquad\qquad\;\; | \qquad\qquad\qquad\;\; | \\ \qquad\qquad\qquad\qquad CH_3 \qquad\qquad\quad CH_2 \cdot C_6H_4 \cdot OH. \end{array}$$

Glycyl-alanyl-tyrosine

It is theoretically possible to lengthen the chain indefinitely. Experimental difficulties, however, multiply rapidly

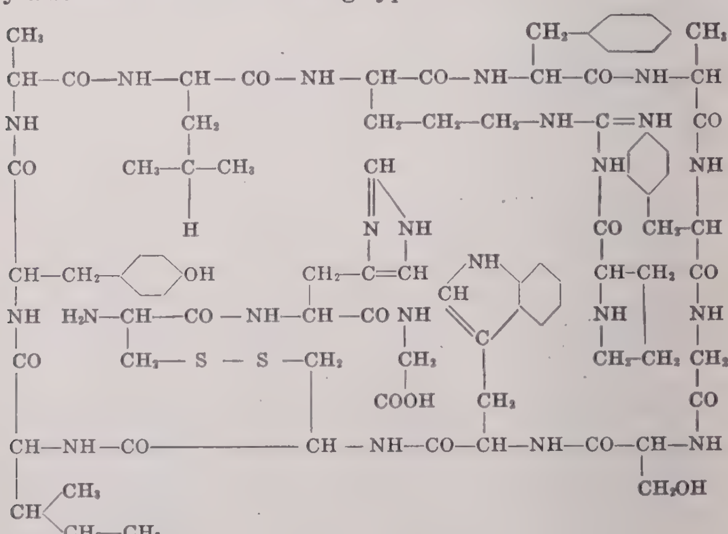
and establish practical limits. By this method, with many ingenious variations, Fischer built up the largest molecule of known structure ever produced by synthetic methods. His greatest achievement was the synthesis of an octadecapeptid (eighteen amino acid molecules combined), a compound with a molecular weight of 1213. It was a colorless, amorphous substance which, in water, gave a highly dispersed colloidal solution with faint opalescence. Like most natural proteins it was precipitated from solution by ammonium sulphate and by tannic acid. There can be no doubt that this compound would have been classified as a protein if it had been discovered in nature instead of appearing as a synthetic preparation.

Since a simple protein is a polypeptid, its formula may be written

$$CHRNH_2 \cdot CO \cdot NH \cdot CHR \cdot CO \cdot NH \cdot CHR \cdot CO \cdot NH \cdots CHR \cdot COOH$$

in which each R represents the residue beyond the α-carbon atom of an amino acid.

To be more specific a protein molecule may be represented by a structure of the following type:



This hypothetical tetradecapeptid may not actually exist. The formula is intended merely to illustrate the polypeptid type of structure.

Hydrolysis by acids, alkalies, or by the ferments of the alimentary tract consists of adding water molecules to the —CO—NH— groups, thus breaking the bonds between carbon and nitrogen with the production of carboxyl and amino groups. As one after another of these groups suffers cleavage the protein molecule is gradually broken into polypeptid fragments. It is not a regular process, resulting in a split at the center of the chain each time, nor is it a uniform erosion of the molecule through the breaking off of terminal groups. Simple and complex hydrolysis products appear together from the beginning of the proteolytic action. Pepsin, of the gastric juice, induces hydrolysis of proteins to a limited extent, giving rise to substances similar to the original protein in general character and composition but of lower molecular weight. These first cleavage products are known as proteoses and peptones. They differ from the parent protein only in degree of molecular complexity and a few properties dependent primarily upon the size of the molecule. A protein, for example, may form an opalescent solution, coagulate when heated, and precipitate in the presence of ammonium sulphate. After treatment with trypsin for a short time it may form an optically clear solution and fail to coagulate on heating but retain all other properties of the original compound. The protein has been converted into proteoses. Further action of trypsin results in the formation of substances still displaying protein characteristics, but which can no longer be salted out of solution by ammonium sulphate. The proteoses have been converted into peptones. As the cleavage proceeds the units become too small to behave like proteins, yet they are more complex than single molecules of amino acids. The polypeptid stage has been reached. Finally the mixture consists of free amino acids, the hydrolysis being complete.

Proteins of the diet reach the blood stream through the walls of the intestine chiefly in the form of amino acids,* and these are recombined within the cells of the body to form the characteristic tissues of the organism. It is evident that the most satisfactory protein diet is one that supplies the different amino acids in the proportions required by the tissues they nourish.

* This statement is disputed by some physiologists. For discussions of the question see Cathcart, The Physiology of Protein Metabolism, and Robertson, Principles of Biochemistry.

Persons who depend entirely upon a vegetable diet must ingest and eliminate excessive amounts of some protein constituents in order to secure the minimum requirement of others. As the food approaches in proximate analysis that of the tissue it builds, the waste in the energy of the system is reduced and at the same time the quantity of food required is diminished. This fact refutes the doctrine of the vegetarian, but it is hardly cogent enough to justify a return to cannibalism.

Many proteins yield decomposition products other than amino acids. Carbohydrates, lipoids, phosphoric acid, nucleic acid, and other types of compounds are liberated by hydrolysis from a great variety of natural proteins.

NUCLEOPROTEINS

Among the important types of complex proteins referred to in the last paragraph the nucleoproteins are preëminent. They are obtained from the nuclei of cells in plant and animal tissues and are composed of simple proteins in combination with nucleic acids. The term, *nucleic acid*, has a rather definite meaning although it is applied to a great variety of compounds. It refers to an acidic hydrolysis product of proteins derived from cell nuclei. It consists of phosphoric acid in combination with at least one purine base, pyrimidine derivatives, and a carbohydrate. The complete hydrolysis of a nucleoprotein is represented by the following diagram. The first cleavage is brought about by gastric digestion and the subsequent processes are due to the action of trypsin and erepsin; or the complete degradation of the molecules can be accomplished artificially by boiling with alkali.

$$
\text{Nucleoprotein}
\begin{cases}
\nearrow \text{Simple protein} \rightarrow \text{polypeptides} \rightarrow \text{amino acids.} \\
\searrow \text{Nuclein}
\begin{cases}
\nearrow \text{Simple protein} \rightarrow \text{polypeptides} \rightarrow \text{amino acids.} \\
\searrow \text{Nucleic acid} \rightarrow
\begin{cases}
\text{phosphoric acid} \\
\text{carbohydrate} \\
\text{purines} \\
\text{pyrimidines}
\end{cases}
\end{cases}
\end{cases}
$$

The carbohydrate derived from most nucleic acids of plant origin is a pentose, *d*-ribose. This sugar, as well as several hexoses, occurs in nucleic acids of animal tissues. Methylpentose, a glucoside derived from pentose by replacement of a

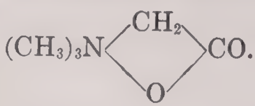
hydroxyl hydrogen atom by the methyl radical, has been identified as a constituent of a few nucleoproteins.

The purine bases found in nucleic acids almost invariably include guanine and adenine. In the pyrimidine group cystosine may be mentioned as the most widely distributed representative. Uracil is found in nearly all vegetable nucleic acids and thymine is present in all nucleoproteins of animal origin.

Amino acids in which methyl groups have replaced the hydrogen attached to nitrogen are called betaines. The simplest member, commonly called betaine, is trimethyl glycine,

$$\begin{array}{l}(CH_3)_3N\text{—}CH_2\text{—}COOH \\ \quad\quad\;\;\;\; | \\ \quad\quad\;\; OH\end{array}$$

or



Although closely related to the ptomaines, produced in the putrefaction of flesh, betaine is not a poison. It occurs in the sap of the sugar beet.

CLASSIFICATION

The configuration of the protein molecule is unknown. That is to say, we do not know the order in which the amino acids are assembled, nor the exact number of them in any particular molecule. Nor do we know the nature of the union between the amino acid groups and such other units as were mentioned in connection with the nucleoproteins. A scientific classification cannot be made until these things have been determined. An arbitrary classification based upon proximate analyses and a few physical properties has been adopted by the American Physiological Society and the American Society of Biological Chemists. It is in reality nothing more than a convenient set of pigeon holes to which the proteins are assigned on the basis of composition or solubility. But it will continue to be useful until we have the data required for the foundation of a systematic classification. It is given below.

Proteins

I. Simple Proteins. Hydrolysis products consist of amino acids only.
  - *a. Albumins.* Soluble in water. Coagulable by heat.
  - *b. Globulins.* Insoluble in water. Soluble in neutral salt solutions.
  - *c. Glutelins.* Insoluble in neutral solvents. Soluble in dilute solutions of acids and bases.

d. Prolamins. Soluble in 70–80 per cent alcohol, insoluble in absolute alcohol, water, and other neutral solvents.

e. Albuminoids. Insoluble in all neutral solvents.

f. Histones. Basic proteins. Soluble in water. Insoluble in dilute ammonia. Form precipitates with solutions of other proteins. Coagulate when heated. Coagulum soluble in very dilute acids.

g. Protamines. Simple polypeptids — not coagulated by heat. Basic amino acids predominate in hydrolysis products.

II. Conjugated Proteins. Hydrolysis products consist of amino acids and at least one other type of molecule.

a. Nucleoproteins. One or more protein molecules combined with nucleic acid.

b. Glycoproteins. Proteins combined with a carbohydrate not included in nucleic acid.

c. Phosphoproteins. Proteins containing phosphorus not included in nucleic acid nor in lecithins.

d. Hæmoglobins. Proteins combined with hæmatin.

e. Lecithoproteins. Proteins combined with lecithins.

III. Derived Proteins. Cleavage products of more complex proteins.

a. Proteans. Insoluble in water. First products of hydrolytic cleavage.

b. Metaproteins. Products formed by further action of acids, alkalies, or enzymes. Soluble in dilute acids and alkalies. Insoluble in neutral solvents.

c. Coagulated Proteins. Insoluble products formed by the action of heat or alcohol on protein solutions.

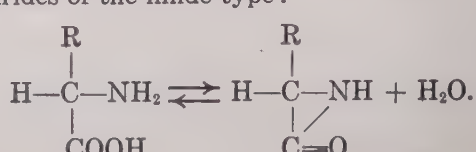
d. Proteoses. Soluble hydrolysis products of proteins. Not coagulated by heat. Precipitated by saturating the solution with ammonium sulphate.

e. Peptones. Hydrolysis products. Soluble. Not coagulated by heat. Not precipitated by ammonium sulphate.

f. Peptides. Definite compounds of known structure consisting of two or more amino acids united through the amino and the carboxyl groups.

The Amino Acids

With few exceptions the α-amino acids are colorless crystalline solids sparingly soluble in water and characterized by high melting points. Some of them are sweet — a rather unusual property in acids. Since they possess the basic amino group as well as the acidic carboxyl, they have a tendency to form anhydrides of the imide type:



Glycine, aminoacetic acid, CH_2NH_2COOH, was first obtained from gelatin by boiling with sulphuric acid. It occurs in very small quantities in vegetable proteins and has not been detected at all in casein nor in albumin. It is abundant in gelatin and in silk fibroin.

Cyanogen is half reduced and half hydrolyzed by hydriodic acid and is thereby converted into glycine.

$$\begin{array}{c} CN \\ | \\ CN \end{array} + 5HI + 2H_2O \longrightarrow \begin{array}{l} CH_2NH_2 \\ | \\ COOH \end{array} + NH_4I + 2I_2.$$

Glycine may be prepared also by Gabriel's synthesis from potassium phthalimide and chloracetic ester.

$$C_6H_4\left\langle\begin{array}{c} CO \\ CO \end{array}\right\rangle NK + ClCH_2 \cdot COOC_2H_5$$

$$\longrightarrow KCl + C_6H_4\left\langle\begin{array}{c} CO \\ CO \end{array}\right\rangle N \cdot CH_2COOC_2H_5 \xrightarrow{H_2O^*}$$

$$C_6H_4(COOH)_2 + NH_2CH_2COOH + C_2H_5OH$$

Alanine, α-aminopropionic acid, $CH_3 \cdot CHNH_2 \cdot COOH$, is widely distributed, being found in almost every known protein. It was synthesized by Strecker (1850) thirty years before it was identified as a protein constituent. His method, which follows, has been applied with equal success in the preparation of many other amino acids:

$$\underset{\text{Acetaldehyde}}{\begin{array}{l} CH_3 \\ | \\ CHO \\ \\ \\ \end{array}} \xrightarrow{NH_3} \underset{\text{Aldehyde ammonia}}{\begin{array}{l} CH_3 \\ | \\ CHNH_2 \\ | \\ OH \end{array}} \xrightarrow{HCN} \underset{\text{Aminocyanhydrin}}{\begin{array}{l} CH_3 \\ | \\ CHNH_2 \\ | \\ CN \end{array}} \xrightarrow{H_2O} \underset{\text{Alanine}}{\begin{array}{l} CH_3 \\ | \\ CHNH_2 \\ | \\ COOH \end{array}}$$

Valine, α-aminoisovaleric acid,

$$\begin{array}{c} CH_3 \\ CH_3 \end{array}\Big\rangle CH \cdot CHNH_2 \cdot COOH,$$

was isolated and its empirical formula was known as early as 1856. Ten years later it was synthesized from valeric acid;

* Best results are obtained by boiling first with dilute sodium hydroxide solution which half hydrolyzes the compound, then completing the hydrolysis by heating with hydrochloric acid.

but the identity of the natural and synthetic products was not established until 1906:

$$\underset{\text{Isovaleric acid}}{(CH_3)_2CH \cdot CH_2 \cdot COOH} \xrightarrow{Br_2} \underset{\alpha\text{-Bromoisovaleric}}{(CH_3)_2CH \cdot CHBr \cdot COOH}$$

$$(CH_3)_2CH \cdot CHBr \cdot COOH \xrightarrow{NH_3} \underset{\text{Valine}}{(CH_3)_2CH \cdot CHNH_2 \cdot COOH.}$$

Leucine, α-aminoisobutylacetic acid,

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>CH \cdot CH_2 \cdot CHNH_2 \cdot COOH,$$

occurs in very large quantities in both animal and vegetable proteins. It is found also in the free state in some organs of the body and in the seeds of many plants. It constitutes 6.6 per cent of gliadin, 19 per cent of zein, 14 per cent of edestin, and more than 9 per cent of casein. It was isolated from meat, cheese, silk, horn, and albumin in the first half of the nineteenth century.

The malonic ester synthesis gives a satisfactory yield.

$$\begin{matrix} COOC_2H_5 \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{matrix} \xrightarrow{Na} \begin{matrix} COOC_2H_5 \\ | \\ CHNa \\ | \\ COOC_2H_5 \end{matrix} \xrightarrow{(CH_3)_2CH \cdot CH_2Br}$$

$$\begin{matrix} COOC_2H_5 \\ | \\ C \\ | \\ COOC_2H_5 \end{matrix}\!\!<\!\begin{matrix} H \\ \\ CH_2CH(CH_3)_2 \end{matrix} \xrightarrow{Br_2} \begin{matrix} COOC_2H_5 \\ | \\ C \\ | \\ COOC_2H_5 \end{matrix}\!\!<\!\begin{matrix} Br \\ \\ CH_2CH(CH_3)_2 \end{matrix} \xrightarrow{H_2O}$$

$$\begin{matrix} COOH \\ | \\ C \\ | \\ COOH \end{matrix}\!\!<\!\begin{matrix} Br \\ \\ CH_2CH(CH_3)_2 \end{matrix} \xrightarrow{\text{heat}} (CH_3)_2CH \cdot CH_2 \cdot CHBr \cdot COOH + CO_2$$

$$(CH_3)_2CH \cdot CH_2 \cdot CHBr \cdot COOH + NH_3 \longrightarrow (CH_3)_2CH \cdot CH_2 \cdot CHNH_2 \cdot COOH + HBr.$$

Isoleucine, α-amino-β-methylvaleric acid,

$$\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>CH \cdot CHNH_2 \cdot COOH,$$

is very similar to leucine in all properties and may be synthe-

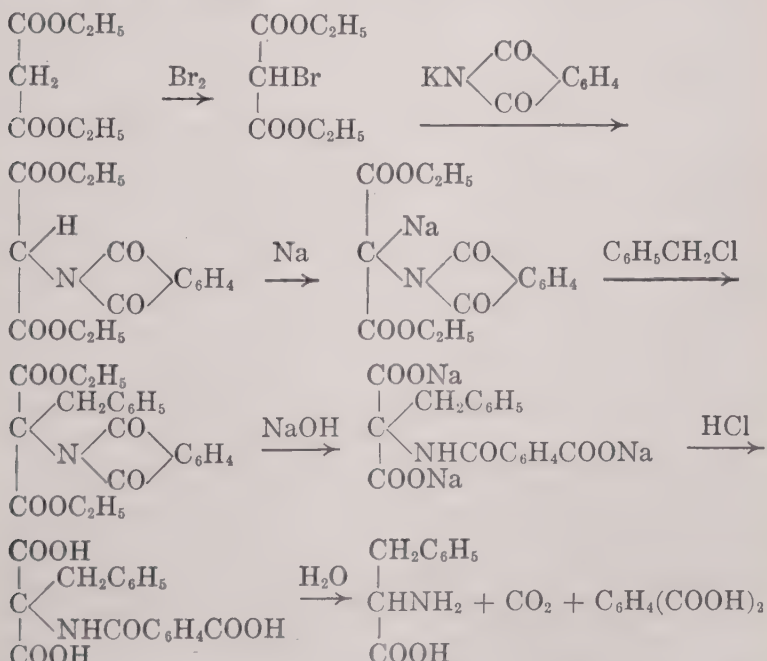
sized in the same way with the substitution of secondary butyl-brom-methane for the isobutyl derivative used in the equations given above. Isoleucine has been prepared also by the action of ammonia on the corresponding chlor-acid and from valeraldehyde through the agency of ammonia and hydrogen cyanide.

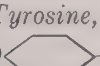
Phenylalanine, β-phenyl-α-amino-propionic acid,

$$C_6H_5 \cdot CH_2 \cdot CHNH_2 \cdot COOH,$$

is found among the hydrolysis products of almost all proteins. Its constitution was proved by Erlenmeyer and Lipp, who produced it from phenylacetaldehyde by an application of the cyanhydrin synthesis.

An ingenious combination of the phthalimide and malonic ester reactions is shown in Sorenson's synthesis of phenylalanine, as indicated below:



Tyrosine, or β-parahydroxyphenyl-α-amino-propionic acid, HO—CH_2CHNH_2COOH, is the first of the amino acids to crystallize from solutions of the hydrolysis products of pro-

teins. Cystine is almost equally insoluble and the two are usually obtained together. Their separation is accomplished by dissolving the tyrosine in dilute nitric acid or by precipitating the cystine in the form of its mercury salt.

Tyrosine was discovered by Liebig among the products obtained by fusing cheese with potassium hydroxide. It crystallizes in fine glossy needles. The simplest synthesis is that of nitrating phenylalanine, reducing the nitro group, diazotizing, and finally decomposing the diazonium salt with warm water.

Serine, α-amino-β-hydroxypropionic acid,

$$CH_2OH \cdot CHNH_2 \cdot COOH,$$

is abundant in silk glue. It is synthesized by the action of sodium ethylate on a mixture of formic and hippuric esters:

$$HC\begin{matrix} /\!\!/O \\ -OC_2H_5 \end{matrix} + C_2H_5ONa \longrightarrow HC\begin{matrix} /ONa \\ -OC_2H_5 \\ \backslash OC_2H_5 \end{matrix}$$

$$\begin{matrix} H \diagdown \\ NaO \diagup \end{matrix} C \begin{matrix} \diagup OC_2H_5 \\ \diagdown OC_2H_5 \end{matrix} + H_2C\begin{matrix} \diagup NH \cdot CO \cdot C_6H_5 \\ \diagdown CO \cdot OC_2H_5 \end{matrix}$$

$$\longrightarrow \begin{matrix} H \diagdown \\ NaO \diagup \end{matrix} C : C \begin{matrix} \diagup NH \cdot CO \cdot C_6H_5 \\ \diagdown CO \cdot OC_2H_5 \end{matrix} + 2C_2H_5OH$$

This product was reduced by sodium amalgam, then hydrolyzed with dilute sulphuric acid:

$$\begin{matrix} H \diagdown \\ NaO \diagup \end{matrix} C : C \begin{matrix} \diagup NH \cdot CO \cdot C_6H_5 + H_2 \\ \diagdown CO \cdot OC_2H_5 \end{matrix}$$

$$\longrightarrow NaO \cdot CH_2 \cdot CH \begin{matrix} \diagup NH \cdot CO \cdot C_6H_5 \\ \diagdown CO \cdot OC_2H_5 \end{matrix} \xrightarrow{H_2O}$$

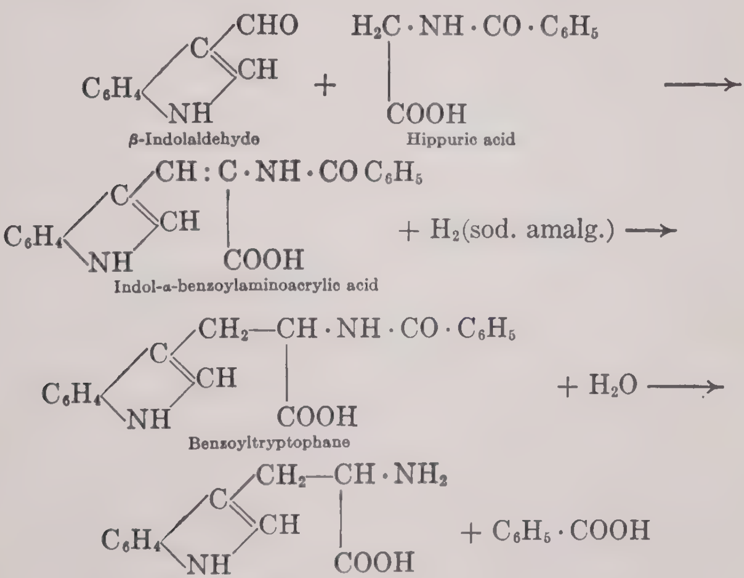
$$HOCH_2 \cdot CHNH_2 \cdot COOH + C_6H_5 \cdot COOH + C_2H_5OH.$$

Cystine, di(β-thio-α-amino-propionic acid), occurs in great abundance in hair, wool, and horn. It is present in all sulphur containing proteins and is the only source of sulphur in many of them. It may be synthesized from serine as follows:

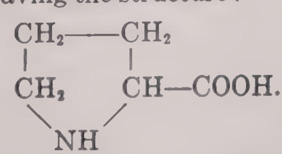
$$\begin{matrix} CH_2OH \\ | \\ CHNH_2 \\ | \\ COOH \\ \text{Serine} \end{matrix} \xrightarrow{P_2S_5} \begin{matrix} CH_2SH \\ | \\ CHNH_2 \\ | \\ COOH \\ \text{Cysteine} \end{matrix} \xrightarrow{HNO_3} \begin{matrix} CH_2—S—S—CH_2 \\ | \qquad\qquad\quad | \\ CHNH_2 \qquad CHNH_2 \\ | \qquad\qquad\quad | \\ COOH \qquad COOH \\ \text{Cystine} \end{matrix}$$

Tryptophane, β-indoxyl-α-amino-propionic acid, is destroyed by acids and by heat and therefore does not appear among the hydrolysis products of proteins unless the decomposition is effected at ordinary temperatures by the action of enzymes. Feeding experiments have demonstrated the fact that animals deprived of tryptophane die within a few weeks. Zein, found in corn, and gliadin of wheat contain no tryptophane. These substances alone, therefore, fail to supply the protein requirements in the diet.

Tryptophane has been synthesized from hippuric acid and β-indolaldehyde.

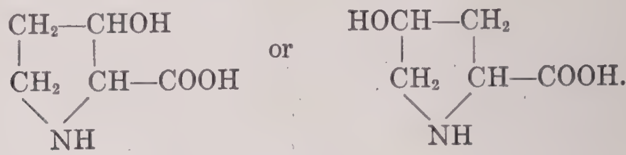


Proline, α-pyrrolidine carboxylic acid,* is the only member of the group which dissolves freely in alcohol. It is a heterocyclic compound having the structure:



* For methods of synthesizing this and the following amino acids and for a more complete discussion of all hydrolysis products of the proteins see Plimmer's Chemical Constitution of the Proteins.

Oxyproline has been isolated from very few proteins and has never been found in large amounts. It is represented by one of the following formulas:



The position of the hydroxyl group has not been determined.

Aspartic, or aminosuccinic acid, occurs in very limited quantities in most proteins. Its amide, asparagine, is abundant in asparagus and in peas and beans. The aspartic acid derived from proteins is lævo-rotatory. Its formula is

$$COOH \cdot CHNH_2 \cdot CH_2 \cdot COOH.$$

Glutamic acid, α-aminoglutaric acid,

$$COOH \cdot CHNH_2 \cdot CH_2 \cdot CH_2 \cdot COOH,$$

occurs in many seeds. Gliadin, from wheat, is 43 per cent glutamic acid. Zein from corn is 26 per cent, and edestin from hemp seed is more than 18 per cent glutamic acid.

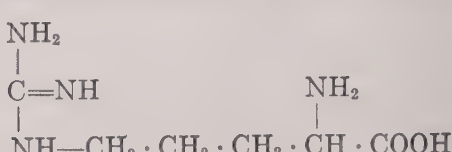
Lysine, α-ϵ-diamino-caproic acid,

$$CH_2NH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHNH_2 \cdot COOH,$$

has not been obtained in crystalline form. It yields a crystalline salt with picric acid and is usually isolated in this form.

Feeding experiments indicate that lysine is of supreme importance to the growing animal organism. Arrested development due to insufficient lysine in the diet has been reported by many investigators.

Arginine, α-amino-δ-guanidine valeric acid, has the structure:



It is a basic substance. It turns litmus blue and forms stable carbonates. The dextro form occurs in nature. Both forms have been prepared in the laboratory.

ISOLATION OF AMINO ACIDS

The protein is hydrolyzed, usually by boiling with 25 per cent sulphuric acid until the mixture no longer responds to the biuret test. The time required varies from a few hours to a week. The solution is then diluted with water, filtered, neutralized with barium carbonate, and separated by filtration from the precipitate of barium sulphate and excess of barium carbonate. The clear filtrate is concentrated by evaporation. The very slightly soluble acids, tyrosine and cystine, crystallize and are removed by filtration.

Diamino acids are precipitated by means of phosphotungstic acid and removed by filtration. The excess of phosphotungstic acid is removed by precipitating it with barium hydroxide, and the excess of barium is removed by means of carbon dioxide. The filtrate from these residues is saturated with hydrogen chloride, and, on standing, glutamic acid crystallizes out. The amino acids remaining in solution are esterified by the action of alcohol and hydrogen chloride. Glycine ester hydrochloride, being only slightly soluble, separates in crystalline form when the alcohol is removed by evaporation. The solution is then neutralized with potassium carbonate, and aspartic ester is extracted with ether. The remaining esters are separated into small groups by fractional distillation under reduced pressure. Fischer tabulates the fractions as follows:

I	50°– 60°	10 mm.	glycine, alanine, leucine.
II	60°– 90°	10 mm.	leucine, valine, proline.
III	90°–100°	0.5 mm.	leucine, proline.
IV	130°–180°	0.5 mm.	phenylalanine, glutamic acid, aspartic acid, serine.

The fractions are separately hydrolyzed, and the free acids in each group are isolated by extraction with various solvents or by fractional crystallization of the free acids or of their copper, silver, lead, or barium salts.

QUALITATIVE REACTIONS

A few qualitative tests are useful in determining whether or not a compound under investigation should be classed as a protein. The following reactions are not exclusively characteristic of proteins. They are tests to which most proteins respond, but for each test substances other than proteins give the same result. If, however, the substance analyzed gives positive response to several of these tests it may be classified as a protein.

1. *Nitric acid.* If a protein solution is carefully floated on the surface of concentrated nitric acid, a white precipitate forms at the junction of the two layers.

2. *Heavy metals.* Most proteins form insoluble salts of lead, copper, and mercury. The precipitate forms in acid, alkaline, or neutral solution.

3. *Alkaloid precipitants.* Phosphotungstic acid, tannic acid, picric acid, phosphomolybdic acid, potassium bismuth iodide, potassium mercuric iodide, and other reagents that precipitate the alkaloids, form insoluble compounds with proteins also.

4. *Biuret reaction.* When dilute copper sulphate solution is added to an alkaline solution of a protein, a reddish violet color is produced. The appearance of the color merely indicates the presence of one of the following groups:

$$—NH \cdot CO \cdot NH \cdot CO—, \quad —NH \cdot CO \cdot CHR \cdot CO \cdot NH—,$$
$$—NH \cdot CO \cdot CO \cdot NH—, \quad —NH \cdot CR_2 \cdot CO \cdot NH—.$$

5. *Glyoxylic acid.* A mixture of a protein solution with glyoxylic acid (or glacial acetic acid which always contains a little glyoxylic acid) is floated on the surface of concentrated sulphuric acid. A reddish violet ring appears at the junction of the liquid layers. The color is due to the presence of tryptophane.

6. *Xanthoproteic test.* Concentrated nitric acid applied to a protein in the solid state imparts a yellow color which changes to orange in the presence of ammonia. The color is due to the presence of a benzene ring, as found in phenylalanine and tyrosine.

7. *Millon's reaction.* Millon's reagent consists of a freshly prepared solution of mercury in nitric acid. It contains mercurous and mercuric nitrates and nitrous and nitric acids. When added to a protein solution, it produces a white precipitate which turns red when heated. The color change is apparently due to the hydroxyphenyl group present in tyrosine. Phenols give the same result.

PROTEIN SALTS

The proteins are amphoteric. Many of them form definite series of salts with acids and with bases. Robertson * has studied the salts of casein, a typical phosphoprotein, obtained from milk by precipitation with dilute acetic acid. Casein, when dry, is a white, amorphous powder. It is insoluble in water but soluble in fifty per cent alcohol. A suspension of casein in water turns litmus red where the suspended particles touch the litmus paper. It also liberates carbon dioxide from

* T. B. Robertson, Physical Chemistry of the Proteins.

carbonates. Osborne * has prepared sodium, potassium, magnesium, and calcium caseinates.

The alkali salts of casein are soluble in water and may be precipitated unchanged by the addition of alcohol. Van Slyke and Bosworth prepared an insoluble salt of casein with calcium hydroxide which contained 11.25×10^{-5} equivalents of the base per gram of the protein, and another salt containing 22.5×10^{-5} equivalents of base per gram of casein. Using sodium or potassium hydroxide, it was found that 11.4×10^{-5} mols of the base would just suffice to dissolve the protein. By means of the hydrogen electrode Robertson measured the changes in potential caused by varying the ratio of casein to potassium hydroxide in solutions in which the electrode was immersed. Plotting these potential differences with reference to the molal concentrations of the base, he found in the curve a series of definite positions of minimum slope corresponding to the values 11.4×10^{-5}, 22.8×10^{-5}, 45.6×10^{-5}, 91.2×10^{-5}, and 182×10^{-5} equivalents of the base per gram of casein. Each of these values is a simple multiple of the smallest quantity. The maximum amount of base absorbed by casein was almost exactly sixteen times the amount required to dissolve the protein. He concluded that at least five potassium salts of casein are formed, the first one containing one and the last sixteen potassium atoms, and in all probability there are at least sixteen different potassium salts of this protein. Similarly the protein molecule is capable of forming series of salts with acids. It was formerly believed that salt formation was due exclusively to the action of bases and of acids on carboxyl groups and amino groups, respectively; but the number of NH_2 groups actually present is too small to account for the quantity of acid neutralized. The total nitrogen content of a protein may be found by ultimate analysis, and the amount present in the form of amino groups may be determined by Van Slyke's method (action of nitrous acid on amines). None of the nitrogen in zein is in the form of free amino groups, and in other proteins the amino nitrogen constitutes a very small percentage of the total nitrogen. In gliadin it amounts to 1.1 per cent, in gelatine 3.1 per cent, casein 5.5 per cent, edestin 1.8 per cent. Similarly, it can be shown that the protein mole-

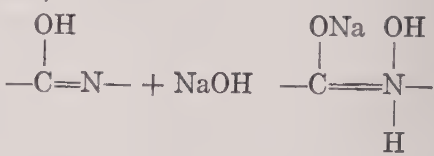
* Osborne, *J. Physiol.*, 27, 398 (1901).

cule does not possess a sufficient number of carboxyl groups to account for the amount of base it neutralizes.

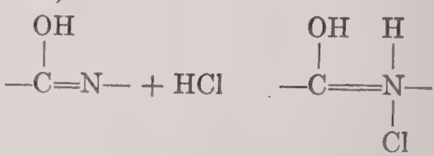
We must conclude that the amphoteric character of the protein is due to the ability of the —CO—NH— groups to combine with acids and with bases. All amides contain this group and are more or less amphoteric. Robertson assumes a keto-enol tautomerism, as indicated below:

Salt formation may then be indicated as a reaction in the enol form:

1. With a base,



2. With an acid,



The protein thus presents as many opportunities for salt formation as there are —CO—NH— groups in the molecule.*

Vitamins

The nutritional requirements of man are completely satisfied by a properly balanced diet composed of proteins, fats, carbohydrates, salts, and water. There are other substances, however, that are essential components of the diet, not because of their nutritive value, but because they prevent the development of certain diseases. Such substances are called vitamins. The constant and almost exclusive use of a single article of diet generally gives rise to nutritional disturbances. The cause of beri-beri, a disease that has taken a heavy toll of life in Japan, China, and India, has been traced to the use of polished rice.

* For opposition to Robertson's theory of protein salt formation see Greenberg and Schmidt, *Proc. Soc. Exp. Biol. and Med.*, **21**, 281 (1924).

The disorder is prevented if whole rice be substituted for the milled product. Well-developed cases of the disease have been cured by the addition of rice bran to the food of the patients. It is evident that the pericarp, or outer layer of the rice kernel, contains some chemical substance which prevents and cures the peripheral neuritis known as beri-beri. The chemical nature of this substance has not been determined. It is present in extremely small quantities in the grain, and attempts to isolate it in a pure state and to determine its chemical constitution have failed. It is simply designated "vitamin B." *

Scurvy is a disease that is due to the lack of vitamin C, a substance present in small but sufficient quantities in most green vegetables and especially abundant in lemons, oranges, and tomatoes.

Normal growth and the maintenance of good health depend also upon the presence in the diet of at least one other substance, known as vitamin A. This is often called the fat-soluble vitamin. It is found in butter and eggs and in most of the animal fats. It is present in some fats of vegetable origin, but not in all of them.†

* Vitamin B has been obtained from many sources including milk, yeast, beans, and peas. The active substance has been concentrated and obtained in solid form. Based upon the composition of such preparations some investigators have proposed definite chemical formulas for the compound. The evidence in support of any formula proposed, up to the present time, is inconclusive. Vitamin B is probably a derivative of pyrimidine.

† For a full discussion of the vitamins and a complete bibliography see Sherman and Smith, The Vitamins.

CHEMISTRY OF LIFE PROCESSES

The earliest distinction between inorganic and organic chemistry was based upon the belief that the compounds synthesized through the agency of living cells were essentially different from those prepared without the aid of vital forces. The preparation of a fat, carbohydrate, or protein from inorganic sources by the artificial methods of the laboratory was considered hopelessly beyond the range of human endeavor. The old belief has been abandoned, for complex organic compounds — the natural products of living tissues — are now being produced by artificial methods in many laboratories. Nevertheless, nature's methods for smoothly converting carbon dioxide and water into carbohydrates, or systematically conducting the asymmetric syntheses of amino acids and then linking them together in definite and orderly sequences to form skin, muscle, hair, nail, or nerve tissue from the same elementary sources, has not yet been duplicated by the comparatively crude technique of the laboratory.

The nitrogen cycle. Plants depend for nourishment upon carbon dioxide, water, and inorganic salts. The nitrogen of the vegetable proteins and alkaloids is derived from inorganic nitrites and nitrates of the soil. The legumes, through the aid of symbiotic organisms in nodules on their roots, are able to utilize atmospheric nitrogen; but most plants must acquire their supply from nitrates. Under the influence of synthesizing enzymes, and of radiant energy, the simple compounds derived from soil solutions and from the air are decomposed in the plant tissues and the elements are reassembled in the form of proteins and other types of simple and complex molecules.

The principal tissues of the animal organism are composed very largely of proteins. Nitrogen is therefore of prime importance in the nutrition of man. But man and the lower animals cannot use free nitrogen nor even nitrates. To them the only suitable source of nitrogen is ready-made protein material. This they derive from plants. Herbivorous animals feed upon

plants and convert the vegetable proteins into the somewhat similar forms of proteins that make up the major part of animal flesh. In the process of digestion the proteins of the diet are hydrolyzed to amino acids and other small units. It is in the form of these small fragments that absorption occurs in the intestine, and from these building stones the characteristic animal proteins are synthesized. Carnivorous animals secure their nitrogen supply from the proteins in the flesh of other animals.

In the course of protein metabolism in the living animal and in the decay of the flesh of dead bodies nitrogen appears in the form of purines, pyrimidines, and other compounds that are capable of conversion into ammonia or ammonium salts by hydrolysis or by reduction. It is through the agency of bacteria that these transformations are made. There exist in the soil also nitrifying bacteria capable of oxidizing ammonium salts into nitrites and nitrates, and thus through the activities of the microscopic forms of life, that stand upon the threshold of both plant and animal domain, the nitrogen of the waste material of animal life is once more made available for the nutrition of plants. The same nitrogen thus plays the same rôles repeatedly; functioning now as living tissue in man, it must later furnish food for the organisms that promote putrefaction and oxidation, then pass into the soil solution to be taken up by plants and to be reconverted into vegetable protein available once more for the nutrition of man.

Carbon and oxygen cycles. Celluloses, starches, and sugars, so abundant in plants, are composed of carbon, hydrogen and oxygen. The carbon utilized by plants in building these carbohydrates is derived from carbon dioxide of the air. Chlorophyll, the green coloring matter of plants, acts as a carrier of carbon dioxide, which is absorbed from the atmosphere, entering the circulatory system of the plant chiefly through the leaves. The absorption and decomposition of carbon dioxide by the green leaves is catalyzed by sunlight. The carbon is retained by the plant tissues, and in connection with water, absorbed through the roots, it is used in synthesizing carbohydrates, proteins, fats, and other types of carbon compounds that are found in the vegetable kingdom. Thus carbon dioxide constitutes the source of carbon that is used by plants in elaborating the compounds destined to serve as food for animals. The oxygen is expelled and returned to the atmosphere to be

inhaled by animals, converted into carbon dioxide, and returned to the atmosphere as a waste product of animal metabolism, ready once more to serve as a food for plants. Some atmospheric oxygen is used by plants in their normal processes of respiration, but it is a small amount as compared with the total volume of oxygen liberated through decomposition of carbon dioxide. Hæmoglobin in the blood of animals, corresponding to chlorophyll in plants, carries oxygen from the lungs to every cell in the body. The animal tissues so carefully elaborated from materials of vegetable origin perform their normal functions for a time, then suffer disintegration and oxidation. The waste products are removed from the system. Carbon in the form of carbon dioxide is carried by the blood back to the lungs and exhaled. Hydrogen is eliminated as water. Nitrogen, with part of the hydrogen, carbon, and oxygen of the worn-out cells, is removed from the body in the form of urea and its derivatives. Thus plants feed upon the waste products of animal life, reconverting the same elements into compounds suitable for the food of other animals, and animals use the carbohydrates, fats, and proteins of plants, discharging them ultimately in forms suitable to nourish other plants.

Respiration. The act of breathing is not regarded, ordinarily, as a direct result of chemical action; yet this may be the case. The respiratory movements of the diaphragm insure a supply of oxygen in the lungs sufficient to aërate the blood. Oxygen diffuses from the lungs into the blood, forming with hæmoglobin the deep red oxyhæmoglobin, and in this form it is carried to every cell in the body. Oxidation processes furnish the necessary energy for muscular activity and for maintenance of the body temperature. Every muscular movement depends upon the release of energy by chemical reactions occurring in the living tissues. It has been determined experimentally that the quantity of energy actually released in the human body through the metabolism of a given weight of sugar or starch is exactly equivalent to the heat evolved when the same weight of carbohydrate is oxidized to carbon dioxide and water by direct combustion in the air.*

When we indulge in vigorous muscular exercise, we breathe more deeply and more rapidly. It is obvious that, since muscular activity is accompanied by oxidation reactions, much

* W. O. Atwater, Year Book, U. S. Dept. Agr., p. 307 (1910).

more oxygen is needed in the system during the periods of increased activity than in periods of repose. But what mechanism insures this fine adjustment between the volume of air drawn into the lungs and the extent of muscular activity?

"There is no immediate or obvious connection between the movements of the respiratory muscles and those of the skeletal muscles. There is no anatomical or mechanical connection between them that would render it *a priori* probable that the motions of the one group of muscles would tend to synchronize in frequency and extent with those of the other. Moreover, the respiratory movements in the adult higher vertebrates are known to be primarily under the control of a particular region of the medulla oblongata, situated in the floor of the fourth ventricle, and designated the respiratory center. Stimulation of this area enhances the rate and amplitude of the respiratory movements. Its narcotization or injury depresses or annuls the respiratory movements. The actual synchrony is therefore not directly between the skeletal muscles and the respiratory muscles, but between the skeletal muscles and the nervous tissues of the respiratory center. Here we have an even less obvious relationship between tissues which nevertheless act in perfect harmony, and the source of this harmony lies in a chemical and not in a spatial or mechanical interdependence of the tissues which participate in it."*

The chemical stimulation of the medulla which gives rise to deeper and more frequent breathing must be due to a change in the composition of the blood. At least two changes occur as a result of enhanced activity: a decrease in oxygen on account of the accelerated rate of oxidation processes, and an increase in carbon dioxide due to its very rapid evolution as an oxidation product. Experiments intended to settle this question were made by operating upon frogs so as to expose the floor of the fourth ventricle of the medulla. When a saturated aqueous solution of carbon dioxide was applied to this area, the animal, although at rest and anæsthetized, breathed more rapidly as if in need of a greater air supply. The experiment did not determine whether the effect was due to carbon dioxide or an increase in hydrogen ion concentration, for weak acids other than carbonic also accelerated the respiratory rhythm. Further proof that the respiration is controlled by chemical action is

* Robertson, Principles of Biochemistry, p. 365.

found in the fact that by crossing the cerebral circulations of two animals, so that the blood from the carotid artery of one animal supplies the brain of the other, any condition imposed upon one of them which would normally change its respiratory rhythm actually produces the effect in the other animal.

Digestion. Almost every phase of the process of digestion represents a type of chemical action. Under the influence of an enzyme, ptyalin, in the saliva, carbohydrate hydrolysis begins in the mouth. The same process is continued for a time in the stomach, for a considerable quantity of saliva is carried along with unchanged carbohydrates. The secretions of the walls of the stomach do not act upon unchanged carbohydrates nor upon the dextrins and maltose formed under the influence of ptyalin, but they do initiate the hydrolysis of proteins converting them into somewhat simpler molecules known as proteoses and peptones. In the intestine carbohydrate, protein, and fat digestion is completed. Pancreatic juice, bile, and ferments derived from the epithelial membrane of the intestinal wall, promote the hydrolytic cleavages that convert the carbohydrates into monoses; the proteins into amino acids and other small molecules; the fats into glycerol and free fatty acids.

The amino acids, absorbed by the intestine and conveyed to the blood stream, are selectively withdrawn from circulation by the various tissues and resynthesized to proteins corresponding in properties to those replaced. The question as to whether a given supply of amino acids shall become muscle, skin, or hair, is determined by the enzymes that bring about condensations of these units. Enzymes are specific in their power to promote hydrolysis of proteins, and it is probably due to specificity of enzyme action that so many different proteins are elaborated from a comparatively small number of amino acids.

Glucose, derived from the carbohydrates of the diet, enters the blood by way of the portal vein and the liver. It is a function of the liver to maintain a constant concentration of glucose (0.10 per cent to 0.15 per cent) in the blood. As rapidly as glucose enters the liver through the portal circulation it is converted into a dextrine-like polymer known as glycogen, and in this form it is stored for future use. Storage of glycogen occurs in the muscles also, but about half of the total supply is held in the liver. To realize the rapidity of the conversion

of glucose to glycogen one has only to remember that the glucose derived from starches and sugars consumed at a single meal may exceed 100 grams. This is all digested and absorbed within three hours without at any time producing a concentration of glucose in the blood higher than the limit specified above. It is, of course, possible to tax the capacity of the liver beyond its power to store carbohydrate; thus a person who consumes half a pound of candy within an hour is likely to produce an abnormal concentration of glucose in the blood (glucohemia).

Fats are hydrolyzed in the intestine under the influence of the pancreatic juice and bile salts. The pancreas furnishes a ferment, lipase, and the bile emulsifies the fat, increasing the surface exposed to the digestive fluids. Both seem to be necessary. In man the bile and the pancreatic ducts unite, so that the secretions from the liver and from the pancreas are mixed before entering the intestine, and no absorption of fat occurs above the point where these fluids enter. Below that point fats appear in the lacteals, the small lymphatic vessels that lead from the intestine to the thoracic duct. In the rabbit the duct from the pancreas enters the intestine some distance below the bile duct; but fats are not absorbed after mixing with the bile until they have passed on to a point below the terminus of the pancreatic duct. Now by a surgical operation the ducts from the pancreas and the liver may be severed and reconnected with the intestine in the reverse positions, so that thereafter fats will be mixed with the pancreatic fluid before encountering the bile. In this case, as before, no absorption occurs until both secretions have had time to act.

The fats are hydrolyzed to glycerol and fatty acids; but in passing through the epithelial lining of the intestine the components are used in the synthetic process of building up the characteristic fats of the body. Differing in this respect from carbohydrates and proteins, they enter the blood stream as fats and not as the hydrolysis products of fats.

In cases of extreme necessity an animal will utilize any fat without taking time to convert it into its own characteristic kind. This does not necessarily imply that the fat is absorbed without previous digestion. A dog's fat melts at 20°, but a dog that had been starved until its reserve store of fat had been exhausted (19 days) and was then fed on mutton tallow (m.p.

40°) until it had gained two or three pounds in weight yielded a fat melting at 40°. But while an experiment of this kind may be of some slight value in showing the capacity of an organism in desperate circumstances to utilize without waste any available food supply, it fails to indicate the normal course of metabolism. Starvation or any serious shock to the nervous system introduces many factors that disturb the normal correlations of the tissues, and observations based upon such experiments often lead to false conclusions.

The heartbeat. As a rule the velocity of a chemical reaction is at least doubled by an elevation of 10° in temperature. Physical changes such as variations in viscosity, surface tension, diffusion, and electrical conductivity have lower temperature coefficients. The frequency of the heartbeat in an animal is influenced by physical as well as chemical forces, and is modified also by nervous stimuli, the emotions, and by the action of narcotics, so that it is not possible to get the temperature coefficient of the heart action by a study of the pulse in connection with fevers. Moreover, there are disorders that cause enormous accelerations of the heart with no elevation of temperature. Hyperthyroidism, for example, may cause the heart to beat more than 200 times per minute without producing any change in the body temperature. But in spite of the numerous unknown factors that influence the cardiac rhythm, it is possible to show that the heart action is modified by temperature changes and that its rate is approximately doubled by an elevation of 10° C.

The heart of an animal may be freed from nervous and emotional influences by removing it from the body and suspending it in a physiological salt solution.* C. D. Snyder discovered that the heart of a turtle may be kept beating in this way for several days, and by warming or cooling the solution in which it is immersed the frequency of the pulsations may be modified. By this method we have obtained the following results with the heart of a Pacific terrapin.

Temperature	10°	15°	20°	25°	30°
Beats per min.	7	12.5	17.5	27	38

* An aqueous solution of salts in such concentrations as to afford the same osmotic pressure as that of the blood, and in such relative proportions as to annul the toxic effects displayed by the separate components.

At 30° the heart beats rapidly for a few minutes, then ceases on account of heat injury.

The embryonic heart of a fish can be observed while still in the egg. The eggs of a marine fish were immersed in sea water at different temperatures by Loeb, who obtained the following results:

Temperature	5°	10°	15°	20°	25°	30°
Beats per min.	19	34.5	60	95	114	180

It seems reasonable to assume, therefore, that this important physiological function of the heart is to some extent under chemical control. Other considerations support this view. A change in the ratio between the quantities of sodium and calcium in the blood affects the cardiac rhythm. In other words, its action is modified by a change in the composition of the blood that circulates through it. The blood vessels also respond to chemical treatment, being dilated by nitrites and constricted by adrenaline. Thus, within certain limits, the blood pressure in the arteries may be controlled by chemical means. Rhythmic pulsations have been observed in chemical reactions not associated with living matter.* They appear to be due to definite correlations between two or more simultaneous reactions. There are, of course, so many unknown factors involved in life processes that it is impossible to assign a single specific cause to any phenomenon presented by living tissue.

Parthenogenesis. The observation made by Loeb and Morgan that cell division occurred in an unfertilized egg of a sea urchin led to a very interesting discovery. Assuming that a chemical substance of some sort must have been responsible for initiating the change, Loeb † sought to reproduce the phenomenon in other eggs by the action of various chemical reagents. It was found that immersion for a brief period in sea water containing a very little ethyl acetate furnished the required stimulus: the eggs being returned to normal sea water developed the fertilization membrane as in the case of natural fertilization. Cell division followed but ceased before the organisms reached the stage of free-swimming gastrulæ. With carefully purified ethyl acetate experiments were less success-

* Bray, *J. Am. Chem. Soc.*, 43, 1262 (1921). Hedges and Myers, *J. Chem. Soc.*, 125, 604 (1924).

† Loeb, Artificial Parthenogenesis and Fertilization, 1913.

ful, and Loeb was led to the conclusion that the required chemical was probably a hydrolysis product of the ester. This proved to be true. Immersion for a few minutes in sea water to which a very little acetic acid had been added caused cell division in more than ninety per cent of the eggs. Propionic, butyric, and valeric acids were equally potent. After many months of patient experimenting a procedure was found that faithfully reproduced all the stages of embryonic development, brought into existence well-developed living organisms, and made it possible to keep them alive and growing for many months. The details relating to the rearing of parthenogenic animals cannot be included here; but the procedure finally adopted for the sea urchin during the first few days is outlined by Robertson as follows: *

> The eggs after extraction from the ovaries and rinsing in filtered sea water are immersed in a mixture of 50 cc. of sea water and 2.8 cc. of tenth normal butyric acid solution, and the mixture is gently agitated to prevent the eggs, which become sticky, from adhering to the vessel. After about two minutes the eggs are collected by gentle rotation of the shallow, flat-bottomed vessel and transferred, by means of a pipette, to normal sea water. If the exposure has been rightly chosen it will be found that the eggs almost immediately form membranes. After allowing them to remain from fifteen to twenty minutes in normal sea water they are again collected in the manner described and transferred to hypertonic sea water, prepared by adding 8 cc. of 2.5 molal sodium chloride solution to 50 cc. of sea water. They are exposed to this addition for a period varying from fifteen to sixty minutes, the optimal exposure varying somewhat with eggs from different females. The eggs are now returned to normal sea water. Within about one hour the first cell division will be observed to have occurred, at the end of forty-eight hours swimming gastrulæ will have been produced, and about two days later plutei with well-developed skeletons.

Other examples of chemical control or correlation are found in connection with the functions of almost every organ of the body. For example, growth and intellectual development are arrested by extirpation of the thyroid gland. Cretinism is a result of its improper functioning. The active secretion of the thyroid seems to be an iodine compound. That its action is of a chemical character is evident, for the ill effects that regularly follow injury or removal of the thyroid may be averted by administration of extracts from thyroid glands of animals.

Lysine, an amino acid found in most proteins, seems to be necessary for normal growth. Young rats deprived of food

* Robertson, Principles of Biochemistry.

containing lysine remained dwarfed for more than a year, but resumed the normal course of physical development when lysine was added to their diet.

The stimulation of the heart by strychnine; depression of the rate of all types of metabolism by morphine; the gradual but certain undermining of the intellectual faculties resulting ultimately in insanity as a result of the continued use of atropine; the anæsthesia produced by chloroform and ether; the wakefulness following the ingestion of caffeine, and the drowsiness produced by chloral; these and a multitude of other definite correlations, including the processes involved in nutrition, growth, development of muscular energy, respiration, and fertilization, indicate that life is dependent upon orderly sequences of chemical reactions.

POLYMETHYLENES

There is a small group of hydrocarbons that may be regarded as occupying an intermediate position between the aliphatic and aromatic types of compounds. They are represented by the formula C_nH_{2n} or $(CH_2)_n$ and are called polymethylenes or cycloparaffins. Although isomeric with the olefins, they lack some of the properties ordinarily found in unsaturated hydrocarbons. Some of them are not oxidized at all by potassium permanganate solutions, whereas hydrocarbons having double bonds are rapidly oxidized by this reagent. They have higher boiling points and lower atomic volumes than the corresponding olefins; and, although the lower members are unstable, they are, as a class, less reactive than hydrocarbons of the ethylene type.

The methods employed in making the polymethylenes indicate that these hydrocarbons are cyclic compounds. Ethylene might be regarded as the first polymethylene as well as the first member of the olefin series; but it is customary to regard trimethylene or cyclopropane as the simplest ring compound.

Cyclopropane, C_3H_6, is prepared by the action of sodium on 1, 3, dibrompropane:

$$CH_2\begin{matrix}\diagup CH_2Br \\ \diagdown CH_2Br\end{matrix} + 2Na \longrightarrow CH_2\begin{matrix}\diagup CH_2 \\ \;\;| \\ \diagdown CH_2\end{matrix} + 2NaBr.$$

It is a gas (m.p. $-126°$, b.p. $-35°$) which, in direct sunlight, absorbs bromine slowly, regenerating trimethylene bromide. With chlorine the reaction is rapid.

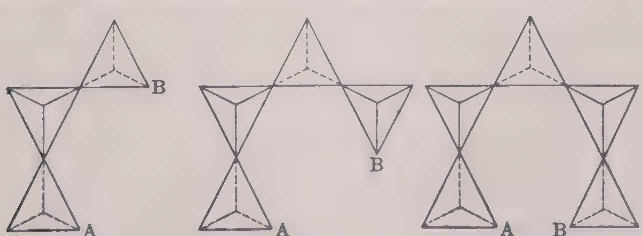
Cyclobutane and *cyclopentane*, low-boiling colorless liquids, have been prepared from tetramethylene dibromide and pentamethylene dibromide respectively.

Cyclohexane, hexahydrobenzene, or hexamethylene, C_6H_{12}, is obtained from benzene, C_6H_6, by reduction with hydrogen. The reaction proceeds under various conditions. Sabatier and Senderens passed a mixture of hydrogen gas and benzene vapor over nickel powder at 150° to 200°. Willstätter passed hydrogen gas into liquid benzene at ordinary temperatures,

using platinum black as a catalyst. The first method is superior from the standpoint of time required and yield obtained.

Cyclohexane resembles benzene in all physical properties. It melts at 6.4° and boils at 80°. Benzene melts at 5.4° and boils at 80.4°. But they differ in chemical properties. Benzene is nitrated by concentrated nitric acid and sulphonated by sulphuric acid. Cyclohexane is not affected by these reagents. Chlorine acts upon the vapor of cyclohexane in sunlight forming monochlorcyclohexane and other products.

The stability of the ring increases as the number of carbon atoms in it increases until that number reaches five or six. There seems to be no measurable difference in the stability of pentamethylene and hexamethylene. But as the number of atoms in the ring increases beyond six the bonds weaken; the compounds become more reactive and show greater tendencies to break up into other types of structure. Baeyer's strain theory applies here as it does in the aromatic series. Baeyer assumed that " the four valences of a carbon atom act parallel to the lines, joining the corners of a regular tetrahedron to its center, making an angle of 109° 28′ with each other. The direction of the valences can be altered, but any such alteration produces a strain whose amount is proportional to the angle through which the valences are diverted."* A cyclic compound in which the angles between carbon bonds are much greater or much less than 109° must be unstable, according to this theory, for an appreciable distortion is necessary in such cases to bring the points of attachment together; and the strain on the bond must be proportional to the distortion of the molecule or the deviation of the angle from 109° 28′. The natural, unstrained positions of atoms in saturated carbon chains may be represented graphically as follows:



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* Baeyer, *Ber.*, 18, 2277 (1885).

In order to bring point B (I) in contact with point A, thus closing the ring, as in cyclopropane, the centers of the three tetrahedra must lie at the corners of an equilateral triangle and the valence bonds must therefore make angles of 60° with each other. This angle differs from 109° 28′ by 49° 28′. The strain in each union is shared by two bonds, so that each bond in trimethylene is diverted from its unstrained position through an angle of 24° 44′. In cyclobutane the diversion is 9° 44′; cyclopentane 0° 44′; cyclohexane − 5° 16′, and in cycloheptane − 9° 33′. The experimental facts are in fair agreement with this theory. However, there is no experimental evidence that a five-membered ring is more stable than a six-membered ring, and, in some reactions, rearrangements occur that must increase the strains in the bonds. Cyclobutanol is converted by oxidation into cyclopropylmethanal:

$$\begin{array}{l} CH_2\text{—}CHOH \\ |\qquad\quad | \\ CH_2\text{—}CH_2 \end{array} \xrightarrow{KMnO_4} \begin{array}{l} CH_2 \\ | \\ CH_2 \end{array}\!\!\!> CH\cdot CHO$$

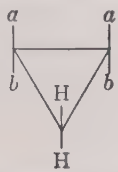
But, on the other hand, cyclobutylcarbinol is changed by warm hydrobromic acid to cyclopentyl bromide.

$$\begin{array}{l} CH_2\text{—}CH\text{—}CH_2OH \\ |\qquad\quad | \\ CH_2\text{—}CH_2 \end{array} \xrightarrow{HBr} \begin{array}{l} CH_2\text{—}CH_2 \\ | \\ CH_2\text{—}CH_2 \end{array}\!\!\!> CHBr$$

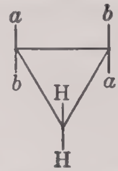
We must conclude that Baeyer's rule for estimating relative stabilities of polymethylene rings is useful but not infallible.

Stereoisomerism. We have traced the cause of geometrical isomerism, which is one type of stereoisomerism, to the presence of a double bond which destroys the power of free rotation of the carbon atoms so joined (p. 33). The classical example of this type of isomerism is found in fumaric and maleic acids. Free rotation is just as effectively arrested by ring formation, and hence we should expect to find examples of space isomers among the substituted cycloparaffins. If we represent the rings by polygons lying in a plane at right angles to the plane of the paper, then the two remaining valences of each carbon atom may be represented by lines in the plane of the paper, one extending above and the other below the plane of the polygon:

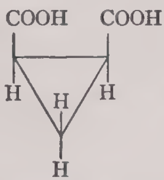
Since the carbon atoms at the corners of the figures cannot rotate independently, a polymethylene having two or more different groups substituted for hydrogen may exist in *cis* and *trans* forms:



and

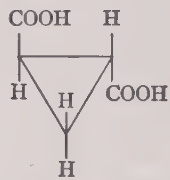


As actual examples we have *cis* and *trans* cyclopropane dicarboxylic acids:



Cis, m.p. 139°

and

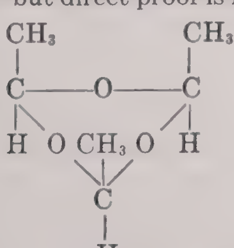


Trans, m.p. 175°

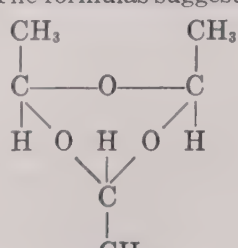
and many derivatives of higher members of the series, including the following:

Name	Cis. M.P.	Trans. M.P.
1, 3 cyclobutane dicarboxylic acid	136°	171°
1, 2 cyclobutane dicarboxylic acid	138	131
1, 2 cyclopentane dicarboxylic acid	140	160
1, 3 cyclopentane dicarboxylic acid	121	88
Hexahydro-orthophthalic acid	192	215
Hexahydro-metaphthalic acid (*)	163	120
Hexahydro-paraphthalic acid	162	300
4 tetrahydro-orthophthalic acid	174	218
3, 5 dihydro-orthophthalic acid	173–175	210
Camphoric acid	188	170

Metaldehyde and paraldehyde (p. 91) may be isomers of this type; but direct proof is lacking. The formulas suggested are:

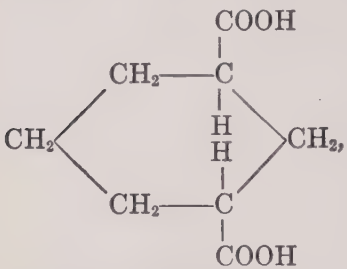


and

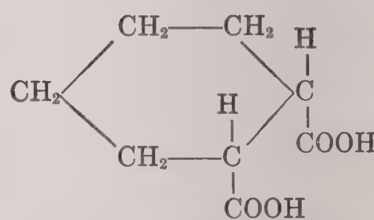


* Metaphthalic and paraphthalic acids are commonly called isophthalic and terephthalic respectively.

Relative asymmetry. The three hexahydrophthalic acids exist in *cis* and *trans* forms, but two of them, namely, hexahydro-orthophthalic acid and hexahydro-metaphthalic acid, differ from the para compound in that each possesses two asymmetric carbon atoms. It can be shown by models that only the *trans* forms display optical activity and are capable of resolution into *d* and *l* modifications. The *cis* forms are inactive on account of internal compensation.

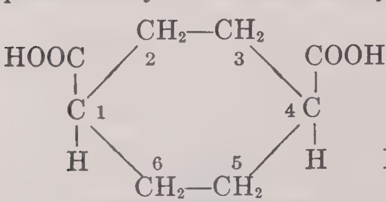


Hexahydro-metaphthalic acid

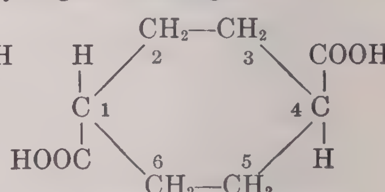


Hexahydro-orthophthalic acid

Baeyer* pointed out that although hexahydro-paraphthalic acid does not have an ordinary asymmetric carbon atom it is, nevertheless, unsymmetrical, for " if a person is represented as floating on his side in the orbit of the ring, with his face to the center; with his feet at 1, and his head at 2, he will, on reaching 4, pass carboxyl on his right and hydrogen on his left; whereas, if he starts with his head at 6 and feet at 1, he will pass carboxyl on his left and hydrogen on his right."



Hexahydro-paraphthalic acid (cis)



Hexahydro-paraphthalic acid (trans)

Baeyer called this *relative asymmetry,* in contradistinction to absolute asymmetry, which is characterized by the attachment of four distinctly different groups to the same carbon atom. Resolution into optically active compounds is impossible in cases of relative asymmetry, for each form is identical with its own mirror-image.

* Baeyer, *Ber.*, **26**, 232 (1893).

AROMATIC COMPOUNDS

HYDROCARBONS

The compounds of the aliphatic series considered in the preceding chapters were regarded as derivatives of methane. In most cases these compounds were represented as having continuous open chains of carbon atoms. Hydrocarbons having the formula C_nH_{2n+2} and their derivatives were called saturated compounds; those corresponding to the formulas C_nH_{2n}, C_nH_{2n-2}, and C_nH_{2n-4} were said to be unsaturated. The aromatic group comprises the derivatives of benzene and some other cyclic compounds. Benzene is the first member of a series of hydrocarbons corresponding to the general formula C_nH_{2n-6}, but it does not act like a highly unsaturated compound. Its six carbon atoms form a closed chain or ring, and this cyclic structure imparts to the molecule properties that would not be predicted from a consideration of the empirical formula alone.

Benzene. Pure benzene is an optically clear, colorless liquid boiling at 80.4° C. and freezing at 5.4°. It has a density of 0.8799 gram per cc. at 20° C. It is practically insoluble in water, but dissolves in all proportions in alcohol and in ether. Benzene burns with a luminous, smoky flame, and on account of its high vapor pressure readily forms explosive mixtures with air. It is an excellent solvent for fats, waxes, and resins. Hundreds of important compounds, including the valuable aniline dyes, and high explosives like picric acid and trinitrotoluene, are derived from benzene.

COAL TAR

The main commercial source of benzene is coal tar. When coal is distilled (that is, heated out of contact with air), a variety of gaseous, liquid, and viscous tarry products are expelled. A solid residue of coke remains in the retort. The process is one

of great industrial value, for coal gas is used in enormous quantities for heating and lighting purposes, while the smelters, and many other concerns operating large furnaces, are dependent upon coke for fuel.

The coal gas is separated from the liquids and tar by means of condensers, and after being freed from ammonia and hydrogen sulphide by washing with water it is conveyed to storage tanks connected with the gas mains of the city. It consists of hydrogen (45 per cent to 50 per cent), methane (30 to 40 per cent), carbon monoxide (6 per cent to 10 per cent), and small quantities of carbon dioxide, nitrogen, acetylene, benzene, and ethylene.

The liquid distillate separates into two layers. The upper layer consists of an aqueous solution of ammonia, ammonium carbonate, ammonium hydrosulphide, pyridine, and some other compounds. This is the most important commercial source of ammonia and all ammonium salts. The lower layer consists of a heavy, dark, oily, or viscous mass known as coal tar. The tar, at one time discarded as a worthless by-product, is now prized as the most valuable source of the aromatic compounds. A partial separation of its components is accomplished by fractional distillation. In the preliminary treatment it is cut into five fractions, as follows:

1. Light oil, 80° to 170°
2. Middle oil, 170° to 230°
3. Heavy oil, 230° to 270°
4. Anthracene oil, above 270°
5. Pitch, a semi-solid residue.

Each fraction is then redistilled from smaller retorts or extracted with various solvents to complete the separation.

The light oil is a dark-colored, mobile liquid, less dense than water. The fraction boiling between 80° and 110° consists chiefly of benzene and toluene. Pyridin, thiophen, and phenol are also present in small amounts. The first two are removed by agitating the mixture with concentrated sulphuric acid in which they dissolve, and the phenol is taken out by shaking the mixture with a solution of sodium hydroxide. The hydrocarbons are washed with water after each treatment to remove the acid or alkali. The next portion (100°–140°) consists principally of benzene, toluene, and xylene. The third division (140°–180°) contains xylene, cumene, ethylbenzene, and mesitylene.

Basic and acidic substances are removed, as indicated above, and the hydrocarbons are redistilled until fractions are obtained that boil within very narrow limits of temperature.

The middle oil (170°–230°) contains naphthalene and phenol with smaller quantities of xylenes. From the heavy oil (230°–270°) phenol, cresol, naphthalene, and anthracene are obtained. Mixtures of the crude coal-tar products are used for preserving timbers from decay, and to protect marine pilings from the ravages of the *Teredo*, *Limnora*, and other organisms that bore into untreated wood. Such mixtures are sold under the name of creosote oil. Anthracene oil (b.p. 270° and above) contains anthracene, phenanthrene, diphenyl, and other hydrocarbons which, when pure, are crystalline solids at ordinary temperatures. Anthracene is used in large quantities in the manufacture of alizarin dyes. The residue of pitch is used in the preparation of asphalt.

Constitution of Benzene

An analysis of benzene indicates that it consists of carbon, 92.31 per cent, and hydrogen, 7.69 per cent. The simplest formula that represents these values is CH. The molecular weight of benzene is 78 and its molecular formula is, therefore, C_6H_6. The saturated aliphatic hydrocarbon (hexane) having six carbon atoms has the formula C_6H_{14}. From a consideration of the empirical formula, C_6H_6, one would conclude that benzene must be a highly unsaturated compound; but as a matter of fact, it acts more like a saturated hydrocarbon. Unlike the members of the acetylene series, benzene is oxidized with great difficulty. Halogen acids, cold sulphuric acid, and concentrated alkalies do not affect it, and powerful oxidizing agents, such as hot chromic acid and potassium permanganate solutions, convert it very slowly into carbon dioxide, water, and other products. The free halogens, chlorine and bromine, react with benzene, forming either substitution products, as with saturated hydrocarbons, or addition products. The ability to form addition products reveals the fact that benzene is actually unsaturated, although its inertness is a property not shared by the unsaturated compounds of the aliphatic series.

Dipropargyl, C_6H_6, a liquid boiling at 85°, and isomeric with benzene, is prepared by a method which indicates that it has the following formula: $CH \vdots C \cdot CH_2 \cdot CH_2 \cdot C \vdots CH$. Its properties are in strict harmony with

this structure. It is highly reactive, easily oxidized, forms addition products with halogens and with halogen acids, and yields metallic derivatives with silver and copper salts. Since benzene is fundamentally different, it cannot be represented by a structure similar to that assigned to dipropargyl.

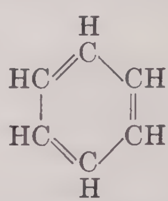
A study of the substitution products of benzene led to the conclusion that its structure must be represented as a closed chain or ring. Some of the evidences in support of this structure will be presented here and corroborating evidence will be found in the sequel.

1. There are no isomeric monosubstitution products of benzene. Only one brombenzene, for example, is known. This is not due to a unique position in the molecule of a single hydrogen atom, making substitution take place in one position only, for all of the hydrogen atoms in benzene are replaceable by the same reagent. Only one conclusion can be drawn from this fact, namely, the six hydrogen atoms in the benzene molecule are similarly placed. In other words, the molecule has a symmetrical structure, with the hydrogen atoms uniformly and equally distributed. This implies the necessity of having one and only one hydrogen atom attached to each carbon atom.

2. There are three isomeric disubstitution products of benzene, whether the substituents are alike or different.

3. There are three trisubstitution products of benzene if the substituents are alike; six if two are alike and one different; ten isomers if the three substituents are all different.

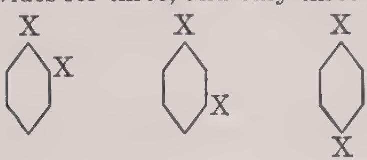
In 1864 Kekulé proposed the following structure to account for the properties enumerated in the last three paragraphs:



The benzene molecule is thus represented as a symmetrical ring or hexagon, with the carbon atoms all alike with respect to positions within the ring, and the hydrogen atoms all similarly located. To determine whether this formula accounts for the substitution products of benzene, let us economize space by writing a hexagon for the formula. The symbol, , will be understood to mean C_6H_6, the six carbon and six hydrogen

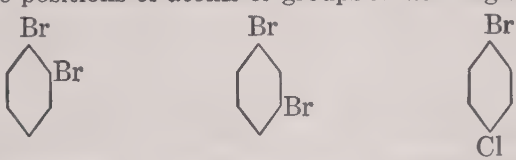
atoms being combined as indicated in the Kekulé formula. Similarly Br will stand for C_6H_5Br, a substitution product derived from benzene by replacing one hydrogen atom by a bromine atom. Using the letter X to represent any atom or radical, we have for any monosubstitution product of benzene the formula X.

Three disubstitution products of benzene can be made and the formula provides for three, and only three:



I II III

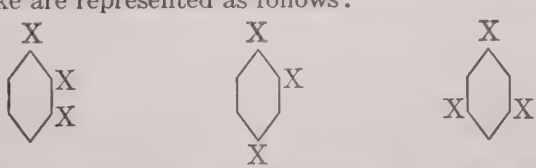
The relative positions of the substituents in formulas I, II, and III are known as ortho, meta, and para, respectively. We specify the positions of atoms or groups in the ring as follows:



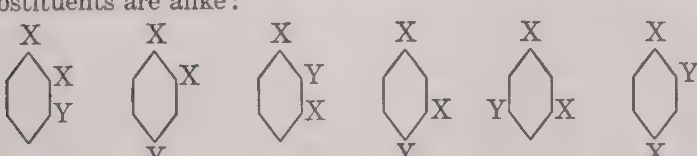
ortho-Dibrombenzene *meta*-Dibrombenzene *para*-Chlorbrombenzene

Obviously, it is immaterial whether the two substituents are alike or different; the possible number of isomers remains the same in either case.

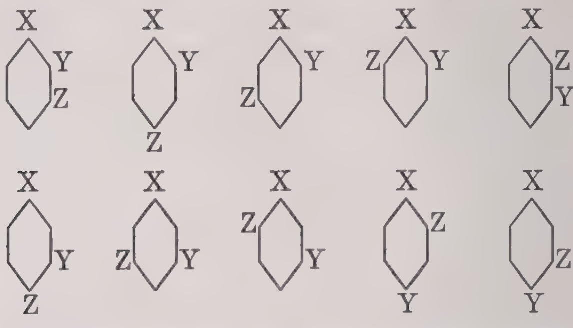
The three possible trisubstitution products if the substituents are all alike are represented as follows:



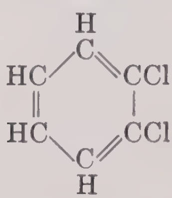
Six trisubstitution products are possible if only two of the substituents are alike:



Ten products if the three substituents are different:

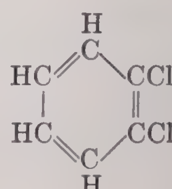


The agreement between the known number of isomers and the number that would be predicted on the basis of a ring structure gave strong support to the views expressed by Kekulé. Not all of the possible compounds have actually been prepared, but in no instance has the ring structure been inadequate to account for known derivatives of benzene. But Kekulé's formula is not entirely satisfactory. This structure should give rise to isomeric *otho*-disubstitution products; for, in one case, the entering atoms or radicals might attach to carbon atoms held together by a single bond, and in the other case to carbon atoms held by a double bond. Thus there should be two *ortho*-dichlorbenzenes:



I

and

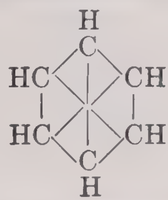


II

No such isomers exist, or, at any rate, no evidence of their existence has been found up to the present time. Kekulé met this objection with the assumption that the double bonds are constantly shifting positions. He maintained that the formula as written above represents a dynamic rather than a static relationship between the atoms. Half the molecules of ortho-dichlorbenzene correspond to formula I and half to formula II, or, in other words, any particular molecule is in the condition represented by formula I, half of the time, and in the other form half of the time. This ingenious explanation has never

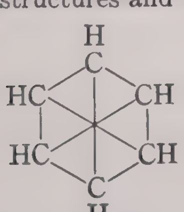
fully satisfied chemists and there has been a perennial crop of new formulas for benzene from Kekulé's time to the present. A few of these inventions deserve consideration.

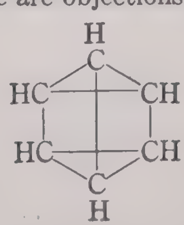
A structure proposed by Armstrong and independently by Baeyer is often called the " centric " formula. In this arrangement one valence bond of each carbon atom is extended toward the center of the ring. The fourth valence of each carbon atom belongs as much to one as to any other carbon atom in the ring, the six tetrahedral carbon atoms being arranged in such a way as to throw the fourth, or unoccupied point, of each tetrahedron toward the center of the group.

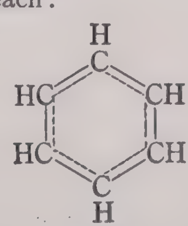


If each carbon atom were independently unsaturated, having one free bond, as indicated in the centric formula, it should be possible to introduce a single halogen or other univalent group, forming a compound of the type C_6H_6X. This is not the case. Invariably the addition products formed belong to the types $C_6H_6X_2$, $C_6H_6X_4$, and $C_6H_6X_6$. But the centric formula affords an explanation of the fact that it is much more difficult to bring about the addition of the first pair of elements than it is to introduce the second and third pairs. If the inactivity of the free valences is due to their symmetrical arrangement, then as soon as two of the bonds have been withdrawn from the central group the symmetry has been destroyed and the remaining bonds are less firmly held in place. They then become as active as ordinary double bonds.

Arguments have been made in support of each of the following structures and there are objections to each:

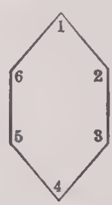

(Claus)

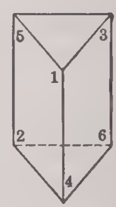

(Ladenburg)


(Thiele)

Thiele's formula is perhaps the best of the group. The dotted lines represent partial valences. They are unreactive, for the formula as a whole is an example of what is known as a conjugated system. The merits and limitations of this structure are discussed under partial valence.

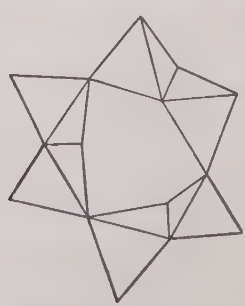
The Ladenburg formula represents the benzene molecule as a triangular prism. This formula provides for the formation of addition products, but only by breaking a single bond between carbon atoms. The number of isomeric forms of polysubstitution products is as well accounted for as by the Kekulé, Baeyer, and Thiele formulas. From the number of trisubstitution products that may be derived from a given disubstitution product it is possible to determine which positions in the Ladenburg formula correspond to the ortho, meta, and para positions of the Kekulé formula. (See Orientation.) For reference the corresponding positions are numbered in the following diagrams.





It should be possible to secure stereoisomeric disubstitution products of benzene, if the hydrocarbon corresponds to the Ladenburg formula, but no such isomerism has been observed.*

On the basis of the Kekulé formula, the arrangement of the atoms, in space, is shown in the following diagram:



* For other objections to this structure and for a more complete discussion of all of these formulas, see Stewart's Stereochemistry.

The centers of the six carbon atoms lie in one plane and no optical isomerism could exist in benzene, nor in any substitution product, even if the six hydrogen atoms were replaced by six different elements. As a matter of fact, no case of optical activity has yet been traced to asymmetry in the benzene nucleus. This, of course, does not exclude from consideration space formulas that present such possibilities; for stereoisomers may exist which we cannot separate nor detect by methods now at our command.

The simple hexagon, , will be used throughout this text as an abbreviation for the structural formula of benzene. The univalent phenyl radical, C_6H_5—, derived from benzene by loss of one hydrogen atom, will be written C_6H_5 — or represented by the symbol  or by the Greek letter ϕ. Thus, brombenzene will be written, C_6H_5Br, Br, or ϕBr; and benzene itself will be written C_6H_6, , or ϕH. Radicals derived from the aromatic hydrocarbons are designated *aryl* radicals.

Homologues of Benzene

By direct or indirect means, the hydrogen atoms in benzene may be replaced by alkyl or aryl radicals, and thus various types of hydrocarbons, genetically related to benzene, may be prepared.

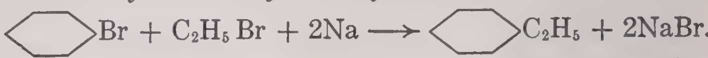
An alkyl radical or other group, attached to the benzene ring in the place of hydrogen, is referred to as a side chain, and the benzene residue is called the nucleus of the molecule.

A side chain may consist of an aliphatic group, as in toluene, $C_6H_5 \cdot CH_3$, or it may be exclusively aromatic in character, as in biphenyl, $C_6H_5 \cdot C_6H_5$, or it may be composed of an aliphatic group in which hydrogen has been replaced by aryl radicals, as in triphenylmethane, $C_6H_5\text{—}CH\!<\!\begin{smallmatrix}\phi\\ \phi\end{smallmatrix}$.

The following general methods are employed in the synthesis of homologues of benzene.

1. The Fittig synthesis. A reaction corresponding to the Wurtz synthesis (p. 23) consists of treating a mixture of an

aryl halide and an alkyl halide with sodium. Thus brombenzene and ethyl bromide yield ethylbenzene.



Mixed products are obtained in this reaction, for ethyl radicals unite, forming butane, $C_2H_5 \cdot C_2H_5$, and phenyl radicals combine to form biphenyl, .

2. **The Friedel and Crafts reaction.** Homologues of benzene may be made also by the action of an alkyl halide on an aromatic hydrocarbon in the presence of dry aluminum chloride.

$$\underset{\text{Benzene}}{C_6H_6} + \underset{\substack{\text{Methyl}\\ \text{bromide}}}{CH_3Br} \longrightarrow \underset{\text{Toluene}}{C_6H_5 \cdot CH_3} + HBr.$$

This is an important general reaction. The aluminum chloride is regarded as a catalyst although in some cases it is necessary to use as many mols of $AlCl_3$ as there are mols of the reacting hydrocarbon, and in many cases there is evidence of the formation of an intermediate product containing aluminum and chlorine.

3. Distillation of an acid with lime gives rise to a hydrocarbon as in the aliphatic series:

$$\underset{\text{Benzoic acid}}{C_6H_5COOH} + CaO \longrightarrow \underset{\text{Benzene}}{C_6H_6} + CaCO_3.$$

4. A mixture of an aromatic hydrocarbon and an alcohol if heated (300°) with zinc chloride in a sealed tube yields a higher hydrocarbon and water:

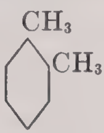
$$C_6H_6 + C_4H_9OH + (ZnCl_2) \longrightarrow C_6H_5 \cdot C_4H_9 + H_2O.$$

Physical constants of a few of the homologues of benzene are given in the following table:

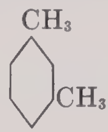
Name	Formula	M.P.	B.P.	Sp. Gr.
Toluene	$C_6H_5CH_3$	−93°	111°	0.8708 (13°)
Xylene (*o*)	$C_6H_4(CH_3)_2$	−28°	142°	0.8932 (0°)
Xylene (*m*)	$C_6H_4(CH_3)_2$	−54°	139°	0.8812 (0°)
Xylene (*p*)	$C_6H_4(CH_3)_2$	+15°	138°	0.8801 (0°)
Hemimellitene	$C_6H_3(CH_3)_3$ 1, 2, 3		175°	
Pseudocumene	$C_6H_3(CH_3)_3$ 1, 2, 4	−57.5°	170°	0.8790 (20°)
Mesitylene	$C_6H_3(CH_3)_3$ 1, 3, 5		164.5°	0.8693 (10°)
Ethylbenzene	$C_6H_5C_2H_5$	−94°	134°	0.8832 (0°)
Cumene	$C_6H_5C_3H_7$ (*iso*)		153°	0.8798 (0°)
Propylbenzene	$C_6H_5C_3H_7$ (*n*)		158.5°	0.8810 (0°)
Cymene	$C_6H_4CH_3C_3H_7$ 1, 4	−73.5°	175°	0.8723 (0°)
Pentamethylbenzene	$C_6H(CH_3)_5$	53°	230°	
Hexamethylbenzene	$C_6(CH_3)_6$	164°	264°	
Hexaethylbenzene	$C_6(C_2H_5)_6$	129°	298°	

Toluene, $C_6H_5 \cdot CH_3$, a mobile, colorless liquid, is obtained from coal tar by distillation, or it may be prepared synthetically by either of the methods given above. It is the source of the high explosive, trinitrotoluene, and of many useful reagents such as benzyl chloride, benzaldehyde, and benzoic acid.

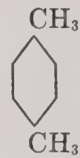
Xylenes. The three xylenes occur in coal tar. They are represented by the following formulas:



Orthoxylene
m.p. – 28°, b.p. 142°



Metaxylene
m.p. – 54°, b.p. 139°

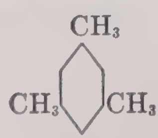


Paraxylene
m.p. 15°, b.p. 138°

The ortho and para xylenes are oxidized by hot dilute nitric acid much more rapidly than is metaxylene. Ortho and meta xylenes are converted into sulphonic acids by sulphuric acid in a shorter time than is required to sulphonate the para compound.

Cymene is found in oil of lemon, oil of eucalyptus, oil of thyme, and in many other essential oils. It may be obtained by heating camphor with phosphorus pentoxide. *Mesitylene* is prepared by mixing acetone with concentrated sulphuric acid and distllling the mixture several hours later. The reaction consists of a condensation of three molecules of acetone with loss of three molecules of water.

Cymene



Mesitylene

Biphenyl, $C_6H_5 \cdot C_6H_5$ (m.p. 71°, b.p. 254°), crystallizes from hot alcohol in large colorless plates. It is formed by passing benzene vapor through a red-hot tube. This is the best laboratory method for making it *:

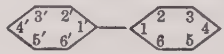
$$2C_6H_6 \longrightarrow C_6H_5 \cdot C_6H_5 + H_2.$$

Sodium acts on brombenzene in ether, producing biphenyl.

$$2C_6H_5Br + 2Na \longrightarrow C_6H_5 \cdot C_6H_5 + 2NaBr.$$

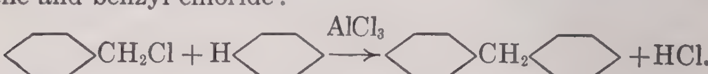
* Fischer, *Anleitung zur Darstellung Organischen Präparate.*

The positions of the carbon atoms in biphenyl are numbered as follows:



Bromine and chlorine form substitution products with biphenyl, the first halogen atom entering the molecule in position 4 (or 4′). On further treatment, a 4, 4′-dihalogen substitution product is formed. Nitric acid converts the hydrocarbon into 2-nitrobiphenyl, 4-nitrobiphenyl, 2, 4′-dinitrobiphenyl, and 4, 4′-dinitrobiphenyl. Chromic acid removes one of the rings, as it would an aliphatic side chain, the principal product formed being benzoic acid, 

Diphenylmethane, $(C_6H_5)_2CH_2$ (m.p. 26°, b.p. 262°), is prepared by the action of aluminum chloride on a mixture of benzene and benzyl chloride:



It is easily oxidized by chromic acid to benzophenone, $C_6H_5 \cdot CO \cdot C_6H_5$. At high temperatures, the vapor of diphenylmethane is decomposed, yielding fluorene and hydrogen:

$$\begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\!\!>\!CH_2 \longrightarrow \begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!>\!CH_2 + H_2.$$

Fluorene melts at 113°, boils at 295°, and forms beautiful fluorescent crystals. On oxidation fluorene yields diphenyleneketone, $\begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!>\!CO$, a compound produced also by distilling the calcium salt of diphenic acid:

$$\begin{matrix} C_6H_4COO \\ | \\ C_6H_4COO \end{matrix}\!\!>\!Ca \longrightarrow \begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!>\!CO + CaCO_3.$$

Fluorene is oxidized by lead dioxide at 330°, forming a bright red, solid hydrocarbon, dibiphenylene-ethylene (m.p. 188°):

$$2\begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!>\!CH_2 \xrightarrow{PbO_2} \begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!>\!C{=}C\!<\!\!\begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}.$$

Triphenylmethane, $(C_6H_5)_3CH$ (m.p. 93°, b.p. 359°), is obtained from chloroform and benzene by Friedel and Crafts' reaction:

$$CHCl_3 + 3C_6H_6 \xrightarrow{(AlCl_3)} CH(C_6H_5)_3 + 3HCl.$$

The hydrocarbon is oxidized by lead dioxide or other mild oxidizing agents to triphenylcarbinol, $(C_6H_5)_3COH$, a colorless crystalline body, melting at 163°. The hydroxyl of the carbinol is, in turn, easily replaced by chlorine through the agency of acetyl chloride or even by hydrogen chloride, and the chloride reverts spontaneously to the carbinol if exposed to moist air. These derivatives of triphenylmethane are important on account of their use in the manufacture of triphenylmethane dyes.

Tetraphenylmethane, $(C_6H_5)_4C$ (m.p. 285°, b.p. 431°), a colorless, crystalline hydrocarbon, insoluble in alcohol, ether, and cold acetic acid, but fairly soluble in hot benzene, may be prepared through the action of phenylmagnesium bromide on triphenylmethylbromide (Grignard reaction):

$$(C_6H_5)_3CBr + C_6H_5MgBr \longrightarrow (C_6H_5)_4C + MgBr_2.$$

The yield is only 5 per cent to 10 per cent of the theoretical. Many unsuccessful attempts to prepare this compound were made during the last half of the nineteenth century. The synthesis was finally accomplished by Gomberg* through the action of phenylhydrazine on triphenylbrommethane:

$$(C_6H_5)_3CBr + H_2N \cdot NH \cdot C_6H_5 \longrightarrow (C_6H_5)_3C \cdot NH \cdot NH \cdot C_6H_5 + HBr.$$

This crystalline product, triphenylmethyl-hydrazobenzene (m.p. 137°), when dissolved in ether, absorbs oxygen from the air, forming triphenylmethyl-azobenzene, a crystalline compound melting at 114° and having the formula

$$(C_6H_5)_3C-N=N-C_6H_5.$$

The latter decomposes between 120° and 130° into nitrogen and tetraphenylmethane.

Tetraphenylethylene (m.p. 221°, b.p. 420°–425°) is a representative aromatic derivative of the unsaturated hydrocarbons.

* Gomberg, *Ber.*, **30**, 2043 (1897).

It is prepared by heating benzophenone chloride* with diphenylmethane:

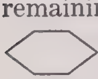
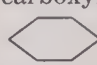
$$(C_6H_5)_2CCl_2 + (C_6H_5)_2CH_2 \longrightarrow (C_6H_5)_2C = C(C_6H_5)_2 + 2HCl.$$

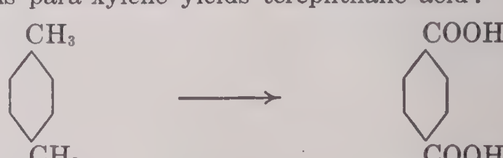
Unlike most unsaturated compounds, this hydrocarbon does not form an addition product with bromine nor iodine nor with halogen acids. Chlorine, however, does react by addition.

Phenylacetylene (b.p. 140°–142°) is made by the removal of hydrogen chloride from acetophenone chloride, through the agency of alcoholic potash:

$$C_6H_5 \cdot CCl_2 \cdot CH_3 + 2C_2H_5OK \longrightarrow C_6H_5 \cdot C \vdots CH + 2KCl + 2C_2H_5OH.$$

This compound acts like other acetylene derivatives, forming addition products readily, and precipitating compounds of silver and copper from ammoniacal solutions of salts of these metals.

Oxidation of side chains. Chromic acid, nitric acid, hot acid or alkaline solutions of permanganates and some other oxidizing agents convert side chains into carboxyl groups. Regardless of the length or structure of the side chain, it is removed in the form of carbon dioxide and water, or other compounds of low molecular weight, leaving only the carbon atom which is attached directly to the nucleus, this carbon remaining as part of a carboxyl group. Thus, toluene, CH_3, ethylbenzene, $CH_2 \cdot CH_3$, and isobutylbenzene, $CH_2 \cdot CH{<}^{CH_3}_{CH_3}$, yield the same compound, benzoic acid, $COOH$, when oxidized. If more than one side chain is attached to the same ring, a polybasic acid is produced. Thus para-xylene yields terephthalic acid:



p-Xylene Terephthalic acid

* Benzophenone (m.p. 48°, b.p. 305°) is made, by Friedel and Crafts' reaction, from benzoyl chloride and benzene.

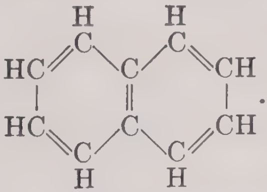
$$C_6H_5COCl + C_6H_6(+ AlCl_3) \longrightarrow C_6H_5 \cdot CO \cdot C_6H_5 + HCl.$$

Phosphorus pentachloride converts this ketone into benzophenone chloride, $C_6H_5 \cdot CCl_2 \cdot C_6H_5$.

Condensed Nuclei

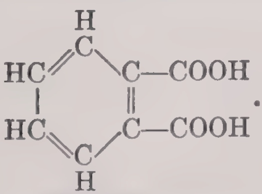
NAPHTHALENE

Naphthalene, $C_{10}H_8$, is obtained from coal tar. It crystallizes from hot alcohol or ether in shining, colorless plates, melting at 80° and boiling at 218°. It is insoluble in water, sublimes slowly at room temperature, distils with steam, and has a characteristic odor. It is used in enormous quantities in the manufacture of the azo dyes, in the preparation of moth balls, in illuminating gas to increase the luminosity of the flame, and in the manufacture of phthalic acid. The naphthalene molecule consists of two benzene nuclei, having two carbon atoms in common:



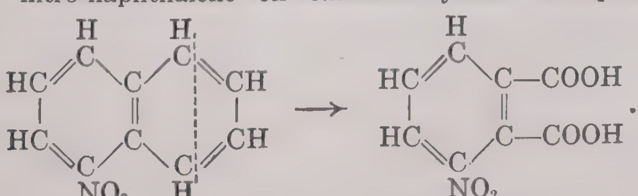
Naphthalene

When oxidized, naphthalene yields ortho-phthalic acid.



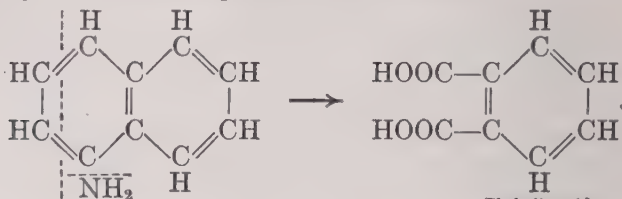
o-Phthalic acid

This indicates that naphthalene contains a benzene ring with two side chains in ortho positions. That the two side chains constitute another benzene ring is shown as follows. Nitro-substitution products of benzene are less susceptible to oxidation than are unsubstituted rings. Amino derivatives of benzene are more easily oxidized than are the unsubstituted rings. Now, nitro-naphthalene on oxidation yields nitro-phthalic acid:



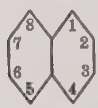
Nitro-phthalic acid

But if the nitro group be reduced to an amino group before the oxidation is effected, then the substituted ring is broken, and ordinary unsubstituted phthalic acid is formed:



Phthalic acid

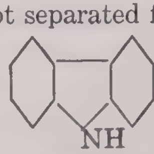
Naphthalene yields two isomeric monosubstitution products; ten disubstitution products if the substituents are alike, and fourteen, if the two entering elements or groups are unlike. The positions in the molecule where substitution may occur are numbered as follows:



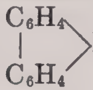
It is obvious that a group attached to carbon atom 1, 4, 5, or 8 makes a compound that is not identical with the substance formed by placing the same substituent in position 2, 3, 6, or 7. The first set of numbers (1, 4, 5, and 8) are called alpha positions, the others are beta positions. Disubstitution products are often designated as ortho, meta, and para, when the substituents are in the same ring, but numbers or letters are used when positions in both rings must be indicated.

At temperatures between 700° and 1000° naphthalene and other aromatic hydrocarbons are formed in small quantities from propane, butane, and other paraffins containing fewer than six carbon atoms, as well as from the higher members of the methane series.*

ANTHRACENE

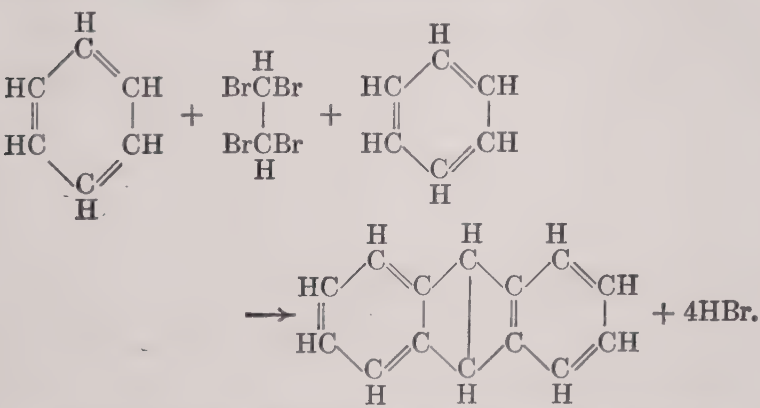
Anthracene, $C_{14}H_{10}$ (m.p. 213°, b.p. 351°), is obtained from coal tar, in which it occurs to the extent of 0.3 per cent to 0.5 per cent. Phenanthrene and carbazole are found in the same fraction and are not separated from anthracene by distillation alone. Carbazole, , is removed by distilling the

* Zanetti, *J. Ind. and Eng. Chem.*, **8**, 674 (1916).

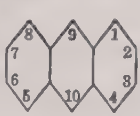
mixture with potassium carbonate. The non-volatile potassium carbazol, , remains in the retort. Phenanthrene is removed by extraction with carbon disulphide, in which it is very soluble.

When exposed to light, anthracene polymerizes to dianthracene, $C_{28}H_{20}$. In the dark this polymer reverts to anthracene. A few other reversible photochemical reactions are known.*

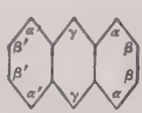
Anthracene may be prepared, by Friedel and Crafts' reaction, from tetrabromethane and benzene:



Other methods of preparation and most of the properties of anthracene indicate that the molecule has the structure given above.† Positions in the molecule are indicated by numbers or by letters:



or

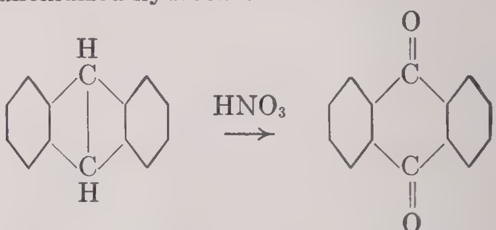


Three monosubstitution products of anthracene may exist, and in many cases the three have been prepared. Fifteen disubstitution products could be made with similar substituents and many more with unlike groups. Not all of these possibilities have been realized.

* Benzaldehydephenylhydrazone, $C_6H_5 \cdot CH{=}N{-}NH \cdot C_6H_5$, (m.p. 152), is a yellow, crystalline compound as ordinarily prepared. In violet light it changes to a scarlet powder which reverts to the yellow form in yellow or green light.

† For opposition to this view see Auwers, *Ber.*, 53, 941 (1920); *ibid.* 58B, 543 (1925).

Anthracene crystallizes in shining, fluorescent leaflets. It is insoluble in water, sparingly soluble in alcohol and ether, but dissolves readily in hot benzene. It forms an insoluble compound with picric acid, $C_{14}H_{10} \cdot C_6H_2(N_nO_2)_3OH$ (m.p. 138°), and a method for the quantitative estimation of the hydrocarbon is based on this reaction. Positions 9 and 10 are very reactive. Sodium amalgam in alcohol causes addition of hydrogen to each of these carbon atoms. Bromine rapidly replaces hydrogen in positions 9 and 10. A satisfactory laboratory method for making hydrobromic acid consists in dropping bromine on anthracene. Nitric acid oxidizes anthracene in positions 9 and 10, forming anthraquinone. The reaction proceeds so rapidly that it is not possible to secure a nitro derivative of the unoxidized hydrocarbon:



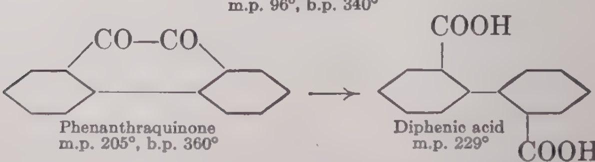
Anthracene Anthraquinone

Further treatment with nitric acid yields nitro derivatives of anthraquinone.

PHENANTHRENE

Phenanthrene, $C_{14}H_{10}$, a coal-tar product isomeric with anthracene, crystallizes in colorless plates and dissolves in alcohol, forming a blue, fluorescent solution. Chromic acid converts it first into phenanthraquinone and ultimately into diphenic acid:

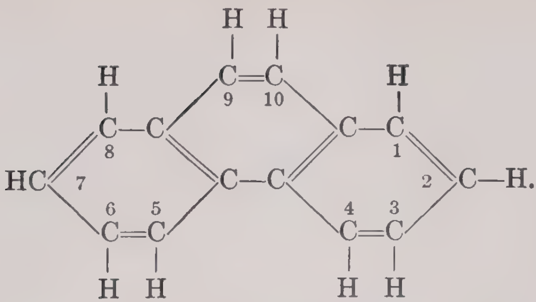
Phenanthrene
m.p. 96°, b.p. 340°



Phenanthraquinone
m.p. 205°, b.p. 360°

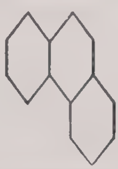
Diphenic acid
m.p. 229°

The carbon atoms that are attached to hydrogen in the phenanthrene molecule are numbered as follows:

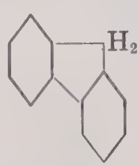


Although anthracene is a very valuable source of alizarine dyes and intermediates, no important uses have been found for its isomer, phenanthrene.

There is a genetic relationship between phenanthrene and fluorene. In composition they differ by one carbon atom:

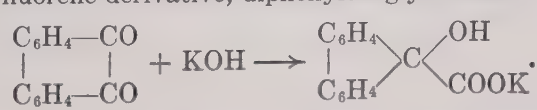


Phenanthrene



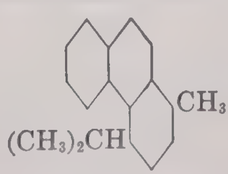
Fluorene

Fusion of phenanthraquinone with potassium hydroxide gives rise to a fluorene derivative, diphenyleneglycolic acid:



This product may be converted into diphenyleneketone by oxidation with potassium permanganate, and the ketone may be reduced to fluorene by means of sodium amalgam.

Reten, a homologue of phenanthrene, occurs in the gum and pitch of spruce and pine trees. It is 1-methyl-4-isopropyl-phenanthrene,



It crystallizes in large leaflets with pearly luster, melts at 98.5°, and boils at 390°. It forms a molecular compound with picric acid that crystallizes in yellow needles, melting at 124°.

Substitution Products of Aromatic Hydrocarbons

ARYL HALIDES

Chlorine and bromine act upon benzene in the presence of sunlight at ordinary temperatures, or without light at temperatures approaching the boiling point of the hydrocarbon, forming addition products of the types $C_6H_6Cl_2$, $C_6H_6Cl_4$, and $C_6H_6Cl_6$. In the presence of certain catalysts (halogen carriers), substitution of the halogen for hydrogen occurs with the formation of compounds of the types C_6H_5Cl, $C_6H_4Cl_2$, and so on to C_6Cl_6. The most effective catalysts are aluminum chloride, iron filings, tin, iodine, and zinc chloride. Aromatic hydrocarbons having aliphatic side chains may be chlorinated either in the ring or in the side chain, the course of the reaction being determined by the control of the experimental conditions. In the absence of direct sunlight and in the presence of a catalyst, substitution occurs in the ring. In sunlight or at high temperatures, in the absence of a catalyst, substitution occurs in the side chain. When chlorine is passed into boiling toluene, practically no substitution occurs in the ring until all of the hydrogen atoms of the side chain have been replaced. The products formed as the reaction proceeds are benzyl chloride, $C_6H_5 \cdot CH_2Cl$, benzal chloride, $C_6H_5 \cdot CHCl_2$, and benzotrichloride, $C_6H_5 \cdot CCl_3$. At a lower temperature, and with the aid of aluminum chloride or iodine, the products successively formed are chlortoluene, $C_6H_4Cl \cdot CH_3$, dichlortoluene, $C_6H_3Cl_2 \cdot CH_3$, and trichlortoluene, $C_6H_2Cl_3 \cdot CH_3$.

In order to secure a product of the type ClCH_2Cl, toluene is treated with chlorine and aluminum chloride at room temperature. The para-chlortoluene thus formed is separated by fractional distillation from other products simultaneously formed, and the purified substance is then subjected to the action of chlorine, without a catalyst and at a higher temperature. Another process of purification is then necessary to separate the required product from compounds having two or three chlorine atoms in the side chain. Aryl bromides are formed in the same way. The iodides are prepared by indirect methods.

Physical constants of a few halogen derivatives of aromatic hydrocarbons are given in the following tables:

Chlorine Compounds

Name	Formula	M.P.	B.P.	Sp. Gr.
Chlorbenzene	C_6H_5Cl	–45°	132°	1.106 (20°)
1, 2-dichlorbenzene	$C_6H_4Cl_2$		179°	1.325 (0°)
1, 3-dichlorbenzene	$C_6H_4Cl_2$	–18°	172°	1.307 (0°)
1, 4-dichlorbenzene	$C_6H_4Cl_2$	53°	173°	1.241 (63°)
1, 2 4-trichlorbenzene	$C_6H_3Cl_3$	16°	213°	1.446 (26°)
Ortho-chlortoluene	$C_6H_4ClCH_3$	–34°	157°	1.085 (18°)
Meta-chlortoluene	$C_6H_4ClCH_3$	–47.8°	162°	1.072 (20°)
Para-chlortoluene	$C_6H_4ClCH_3$	7°	162°	1.071 (18°)
Benzyl chloride	$C_6H_5CH_2Cl$	–41.2°	176–9°	1.103 (18°)
Benzal chloride	$C_6H_5CHCl_2$	–16°	213°	1.295 (16°)
Benzo-trichloride	$C_6H_5CCl_3$	–21.2°	213–4°	1.38 (15°)

Bromine Compounds

Name	Formula	M.P.	B.P	Sp. Gr.
Brombenzene	C_6H_3Br	– 31°	155°	1.491 (20/4°)
1, 2-Dibrombenzene . .	$C_6H_4Br_2$	– 1°	224°	2.003 (0°)
1, 3-Dibrombenzene . . .	$C_6H_4Br_2$	+ 1°	220°	1.955 (19°)
1, 4-Dibrombenzene . .	$C_6H_4Br_2$	89.3°	219°	2.220 (20°)
1, 2, 3-Tribrombenzene . .	$C_6H_3Br_3$	87°		
1, 2, 4-Tribrombenzene .	$C_6H_3Br_3$	44°	276°	
1, 3, 5-Tribrombenzene .	$C_6H_3Br_3$	120°	278°	
Ortho-bromtoluene . . .	$C_6H_4BrCH_3$	– 26°	181°	1.422 (20°)
Meta-bromtoluene . . .	$C_6H_4BrCH_3$	– 39.8°	184°	1.410 (20°)
Para-bromtoluene . . .	$C_6H_4BrCH_3$	28.2°	185°	1.392 (20°)
Benzyl bromide	$C_6H_5CH_2Br$	– 3.9°	199°	1.438 (22°)
Ortho-xylyl bromide . .	$C_6H_4CH_3CH_2Br$	21°	217°	1.380 (22°)
Dibrom-meta-xylene . .	$C_6H_2Br_2(CH_3)_2$ 4, 6–1, 3	72°	256°	
Tribrom-mesitylene . . .	$CBr_3(CH_3)_3$ 2, 4, 6–1, 3, 5	224°		

Chlorbenzene. Phenyl chloride, C_6H_5Cl, a colorless liquid having an agreeable odor, boils at 132° and melts at –45°. It is insoluble in water, but dissolves in all proportions in alcohol and in ether. It is prepared (1) by direct chlorination of benzene, or (2) by the action of phosphorus pentachloride on phenol, or (3) by warming benzene diazonium chloride with cuprous chloride.

1. $$C_6H_6 + Cl_2 \longrightarrow C_6H_5Cl + HCl;$$
2. $$C_6H_5OH + PCl_5 \longrightarrow C_6H_5Cl + POCl_3 + HCl;$$
3. $$C_6H_5N_2Cl + CuCl \longrightarrow C_6H_5Cl + N_2 + CuCl.$$

The second equation represents a method that is not very useful. The hydroxyl group in a phenol is not easily replaced, even under the influence of a powerful reagent like phosphorus pentachloride. In this respect phenols differ from alcohols.

Brombenzene. Phenyl bromide, C_6H_5Br, resembles chlorbenzene in most respects and is prepared by similar methods. It melts at $-31°$, boils at 155°, and has a specific gravity of 1.49 at 20°.

Iodobenzene. Phenyl iodide, C_6H_5I, is a colorless liquid having a density of 1.861 at 0° C. It melts at $-29.8°$ and boils at 188°. It is usually prepared by means of the diazo reaction. Benzene diazonium chloride is warmed with potassium iodide:

$$C_6H_5N_2Cl + KI \longrightarrow C_6H_5I + N_2 + KCl.$$

Iodine does not act upon benzene at low temperatures, but the preparation of C_6H_5I can be accomplished by heating a mixture of benzene, iodine, and iodic acid in a sealed tube. The hydrogen iodide formed is oxidized to iodine and water by the iodic acid, and reversal of the process of substitution is thus prevented.

Phenyl iodide chloride. When chlorine is led into a solution of phenyl iodide in chloroform, a yellow crystalline precipitate is produced corresponding to the formula $C_6H_5ICl_2$. The chlorine is believed to be attached to iodine and not to carbon, for it is very easily removed by gently warming the compound with a solution of potassium iodide. Phenyl iodide is regenerated:

$$C_6H_5ICl_2 + 2KI \longrightarrow C_6H_5I + 2KCl + I_2.$$

If warmed with a dilute aqueous solution of sodium hydroxide, iodosobenzene is formed:

$$C_6H_5ICl_2 + 2NaOH \longrightarrow C_6H_5IO + 2NaCl + H_2O.$$

The iodosobenzene, a yellow, amorphous solid, is readily oxidized by bleaching powder to iodoxybenzene, $C_6H_5IO_2$, a colorless crystalline body that explodes when heated to 236°. Iodoxybenzene is decomposed by hydrogen peroxide, with an evolution of oxygen, and by hydrochloric acid, with the production of chlorine. It liberates iodine from an acid solution of potassium iodide:

$$C_6H_5IO_2 + 2H_2O_2 \longrightarrow C_6H_5I + 2H_2O + 2O_2;$$

$$C_6H_5IO_2 + 4HCl \longrightarrow C_6H_5ICl_2 + 2H_2O + Cl_2;$$

$$C_6H_5IO_2 + 4KI + 4CH_3COOH \longrightarrow C_6H_5I + 4CH_3COOK + 2H_2O + 2I_2.$$

Iodinium compounds. Iodine forms a great variety of organic derivatives. Those of the type ϕ_2IX are known as iodinium compounds. An aqueous solution of the free base diphenyliodinium hydroxide may be prepared by treating a mixture of iodosobenzene and iodoxybenzene with moist silver oxide:

$$C_6H_5IO + C_6H_5IO_2 + AgOH \longrightarrow (C_6H_5)_2IOH + AgIO_3.$$

The solution acts like a base and from it salts of all the common inorganic acids have been prepared. The iodide, for example, is a yellow solid which

crystallizes from hot alcohol in the form of fine needles. When heated, it decomposes into phenyl iodide, no other product being formed:

$$(C_6H_5)_2I \cdot I \longrightarrow 2C_6H_5I.$$

SULPHONIC ACIDS

Fuming sulphuric acid acts upon aromatic hydrocarbons, forming sulphonic acids. Ordinary concentrated sulphuric acid accomplishes the same thing but requires a higher temperature and a longer time:

$$C_6H_6 + H_2SO_4 \longrightarrow C_6H_5 \cdot SO_3H + H_2O.$$

If fuming sulphuric acid is used at a high temperature, two or even three hydrogen atoms may be replaced by SO_3H groups; but not more than three sulphonic acid groups can be introduced into one ring. The formation of benzenetrisulphonic acid is catalyzed by silver sulphate.

The sulphur atom is linked to carbon directly and not through oxygen, as indicated by the fact that thiophenol, C_6H_5SH, when oxidized, yields the same benzenesulphonic acid that is produced by the action of sulphuric acid on benzene.

The free aromatic sulphonic acids are colorless, crystalline compounds. They are soluble in water and most of their metallic derivatives are soluble. The separation of benzenesulphonic acid from the excess of sulphuric acid used in the reaction is accomplished by diluting the mixture and neutralizing it with the carbonate of calcium, barium, or lead. The salt of the sulphonic acid is soluble. It is freed from the precipitated sulphate by filtration and obtained in crystalline form by evaporation of the filtrate. The free acid is obtained from the salt by distillation with the calculated quantity of sulphuric acid.

The free acid or the salt may be converted into an acid chloride by treatment with phosphorus pentachloride:

$$C_6H_5 \cdot SO_2ONa + PCl_5 \longrightarrow C_6H_5 \cdot SO_2Cl + NaCl + POCl_3.$$

Benzenesulphonyl chloride is an oily liquid, sp. gr. 1.384, m.p. 14.5°, b.p. 251.5°. Corresponding derivatives of the homologues of benzene are solids at room temperature. From them the sulphonic amides are prepared by the action of ammonia or ammonium carbonate:

$$C_6H_5 \cdot SO_2Cl + 2NH_3 \longrightarrow C_6H_5 \cdot SO_2NH_2 + NH_4Cl.$$

Benzenesulphonyl chloride is a valuable reagent for use in the separation and identification of amines. (See p. 74.)

Groups that cannot be substituted for hydrogen directly may often be introduced into the ring through the agency of sulphonic acids. This is, in fact, one of the most important applications of sulphonation in the aromatic series. The hydroxyl group is introduced by fusing the potassium salt of a sulphonic acid with potassium hydroxide. Many phenols and naphthols are prepared commercially by means of this reaction:

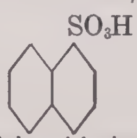
$$C_6H_5 \cdot SO_3K + KOH \longrightarrow C_6H_5OH + K_2SO_3.$$

Nitriles are formed by fusing the salt of a sulphonic acid with potassium cyanide:

$$C_6H_5 \cdot SO_3K + KCN \longrightarrow C_6H_5 \cdot CN + K_2SO_3.$$

Sodium amide serves to introduce the amino group, and in many cases concentrated nitric acid substitutes the nitro group for the SO_3H radical.

Naphthalenesulphonic acids are formed by the direct action of sulphuric acid upon naphthalene. When the reaction occurs at temperatures below 100° α-naphthalenesulphonic acid is the principal product. Higher temperatures promote the production of the β-derivative.



α-Naphthalenesulphonic acid
m.p. 90°

β-Naphthalenesulphonic acid
m.p. 161°

They are colorless, crystalline, deliquescent compounds.

NITRO–COMPOUNDS

Direct nitration of an aromatic compound is accomplished by the action of concentrated nitric acid or a mixture of nitric and sulphuric acids:

$$C_6H_6 + HNO_3 \longrightarrow C_6H_5NO_2 + H_2O.$$

Dilution with water promotes ionization of the nitric acid and retards the change. Hydroxyl groups and not hydrogen ions must be furnished by the nitric acid. By using a large excess of sulphuric acid to absorb the water formed in the reaction, the quantity of nitric acid may be reduced to the theoretical requirement as calculated from the equation. This is

a matter of economic importance since nitric acid is much more expensive than sulphuric.

Nitration is effected at temperatures as low as possible, for nitric acid is a vigorous oxidizing agent and may decompose the compound under treatment. The oxidizing action is accelerated more rapidly by elevating the temperature than is the nitrating effect. At temperatures below zero, it is possible to nitrate some aromatic aldehydes without converting the aldehyde group to carboxyl. Aliphatic hydrocarbons require high temperatures for nitration, and in such cases oxidation is checked by using dilute acid. Many derivatives of benzene require a high temperature and high concentration of acid to accomplish nitration, and in such cases there is usually considerable loss of material through oxidation.

Groups already in the ring influence the rate of nitration. Groups that orient the entering substituent to the meta position retard nitration, and groups that orient to the ortho and para positions facilitate the reaction. (See Brown-Gibson rule.) The first nitro group is easily introduced into the ring, even in the presence of a small amount of water. To place a second nitro group in the same ring one must use concentrated acid. A third nitro group enters only at higher temperatures, and not more than three such groups may be introduced by direct nitration. Similarly, benzoic acid, C_6H_5COOH, resists nitration; but, on the other hand, phenol, C_6H_5OH, can be nitrated by cold, dilute nitric acid.

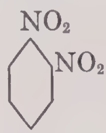
Homologues of benzene, having aliphatic side chains, are nitrated in the ring by cold, concentrated nitric acid, or in the side chain by hot, dilute acid.

Nitrobenzene, $C_6H_5NO_2$, is a pale yellow liquid, m.p. 5.5°, b.p. 210°, sp. gr. 1.204 (20/4°). It is practically insoluble in water. It dissolves in alcohol and in concentrated sulphuric acid, but separates unchanged when the solvent is diluted with water. Nitrobenzene is used to some extent in the manufacture of perfume. Its odor resembles that of almonds. It is the chief commercial source of aniline, and is manufactured in large quantities for the production of aniline dyes.

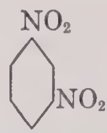
Equal volumes of concentrated nitric and concentrated sulphuric acids are mixed and cooled to 50°. Benzene is then added very slowly and with constant agitation. The mixture is stirred and maintained at 50° for about an hour, then poured into a large volume of cold water. Nitrobenzene

forms a liquid layer under the water. After washing it free from acid and drying with calcium chloride, it is distilled.

Dinitrobenzene. In the ordinary process of making mononitrobenzene, a small quantity of dinitrobenzene appears as a by-product. To make dinitrobenzene the principal product, it is necessary to nitrate at a higher temperature or to employ fuming nitric acid. Three compounds corresponding to the formula $C_6H_4(NO_2)_2$ are known; but if prepared by direct nitration of benzene, the meta compound constitutes by far the greater part of the yield:



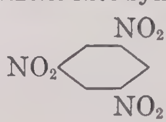
o-Dinitrobenzene
m.p. 118°, b.p. 319°



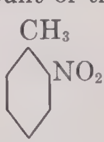
m-Dinitrobenzene
m.p. 91°, b.p. 297°

p-Dinitrobenzene
m.p. 172°, b.p. 298°

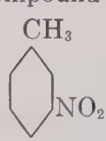
A mixture of concentrated nitric and fuming sulphuric acids converts meta-dinitrobenzene into symmetrical trinitrobenzene,



Nitrotoluenes. The first products obtained in the nitration of toluene are para-nitrotoluene and ortho-nitrotoluene. A very small amount of the meta compound is generally formed also:



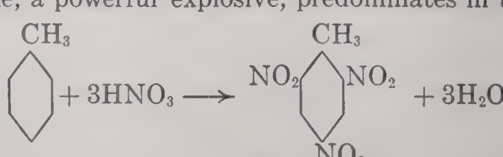
o-Nitrotoluene
m.p. 10.5°, b.p. 218°



m-Nitrotoluene
m.p. 16°, b.p. 230°

p-Nitrotoluene
m.p. 54°, b.p. 234°

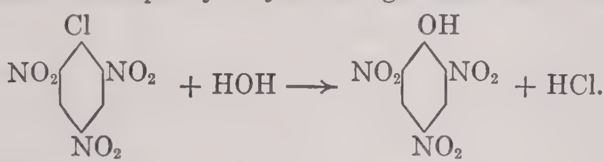
Further nitration produces dinitro bodies, and finally one or more of the six isomeric trinitrotoluenes. Symmetrical trinitrotoluene, a powerful explosive, predominates in the mixture.



Toluene *Sym*-trinitrotoluene

It was manufactured in enormous quantities for use in the war of 1914–1918. It was commonly called T.N.T. The substance is a fairly stable, pale yellow solid. It can be handled safely, for it is not detonated by an ordinary shock. Shells filled with trinitrotoluene may be fired from cannon without exploding, the explosion being induced later through the agency of powerful detonators in connection with timed fuses.

Elements or groups attached to carbon atoms in the ring are less firmly held in nitro compounds than they are in benzene derivatives that have not been nitrated. Thus in chlorbenzene, C_6H_5Cl, the chlorine atom is so firmly held that boiling with an aqueous solution of potassium hydroxide fails to remove it. On the other hand, trinitrochlorbenzene yields its chlorine in a simple hydrolysis through the action of hot water:



Trinitrochlorbenzene Picric acid

Hydrogen atoms as well as halogens become more reactive under the influence of the nitro groups. Trinitrobenzene is easily oxidized to picric acid; but benzene is not converted into phenol by the same process. Finally, a nitro group is itself rendered more reactive by the presence of other nitro groups in the same ring. Mononitrobenzene does not react with alcoholates; ortho- and para-dinitrobenzenes and symmetrical trinitrobenzene react readily with alcoholates, substituting an alkoxyl group for one of the nitro groups. Meta-dinitrobenzene, however, does not respond in the same way:

$$C_6H_4{<}^{NO_2}_{NO_2} + C_2H_5ONa \longrightarrow C_6H_4{<}^{OC_2H_5}_{NO_2} + NaNO_2.$$

Ortho or para

Similarly, one of the NO_2 groups may be replaced by OH or NH_2, by boiling with sodium hydroxide or with an alcoholic solution of ammonia.

DERIVATIVES OF NITROBENZENE

Nitrosobenzene, $C_6H_5 \cdot NO$, exists at low temperatures in the form of large, colorless, monoclinic crystals melting to

an emerald green liquid at 67.8°. It is the first reduction product of nitrobenzene, but cannot be isolated from a reducing medium, since it is rapidly converted to β-phenylhydroxylamine, $C_6H_5 \cdot NHOH$. The reaction is, therefore, allowed to proceed to the β-phenylhydroxylamine stage, and this compound is then oxidized to nitrosobenzene by means of cold chromic acid. Nitrosobenzene explodes when heated with oxygen under twenty-five atmospheres of pressure. It combines with aniline, forming azobenzene, $C_6H_5—N{=}N—C_6H_5$, with phenylhydroxylamine, forming azoxybenzene,

$$\begin{array}{c} C_6H_5—N—N—C_6H_5, \\ \diagdown\!\diagup \\ O \end{array}$$

and with hydroxylamine forming diazobenzene,

$$C_6H_5—N{=}N—OH.$$

In each of these reactions water is formed also.

Azoxybenzene,

$$\begin{array}{c} C_6H_5—N—N—C_6H_5, \\ \diagdown\!\diagup \\ O \end{array}$$

crystallizes from hot alcohol in the form of pale yellow needles, melting at 36.2.° It is obtained by oxidizing aniline with a solution of potassium permanganate in alcohol, or by reducing nitrobenzene with hot alcoholic potash.

Azobenzene, $C_6H_5—N{=}N—C_6H_5$ (m.p. 68°, b.p. 295°), prepared by reducing nitrobenzene with sodium stannite ($SnCl_2$ in excess of NaOH), crystallizes in orange-red leaflets. It is insoluble in water; soluble in alcohol and ether.

Hydrazobenzene, $C_6H_5 \cdot NH \cdot NH \cdot C_6H_5$ (m.p. 131°), is a colorless, crystalline compound which decomposes below its boiling point and is converted by mild oxidizing agents, such as ferric chloride or even atmospheric oxygen to azobenzene. In the presence of a strong acid it undergoes the Hofmann rearrangement, yielding benzidine.

β-Phenylhydroxylamine, $C_6H_5 \cdot NHOH$, a colorless, crystalline substance melting at 81°, is obtained from nitrobenzene by the action of zinc dust and hot water or by the electrolytic reduction of nitrobenzene.

Aniline, $C_6H_5 \cdot NH_2$, is the final reduction product of nitrobenzene. It is a compound of very great importance on

account of its useful derivatives. It is described in connection with the aromatic amines and the dyes.

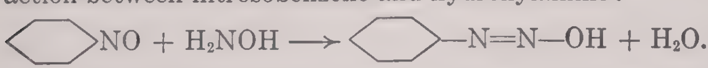
REDUCTION OF NITROBENZENE

In any reduction process nitro compounds yield mixed products; but, by proper control of the conditions, it is possible to make any required type of product predominate. The ultimate reduction product of a nitro-compound is an amine, and if a vigorous reducing agent is employed, this is obtained whether the reaction is carried out in acid, neutral, or alkaline solution. The intermediate products, however, are different in three cases. By suitable choice of reducing agent and careful control of the hydrogen or hydroxide ion concentration the various intermediate products may be isolated.

In the first stage, nitrobenzene is converted into nitrosobenzene:


(1)

Nitrosobenzene is reduced much more rapidly than is nitrobenzene. Therefore, it can never accumulate in the reaction mixture. Its transitory existence is proved by the fact that when nitrobenzene is reduced in the presence of hydroxylamine, diazobenzene is formed. This must be accomplished by a reaction between nitrosobenzene and hydroxylamine:


(2)

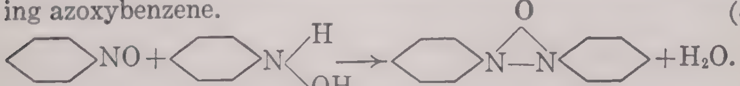
β-Phenylhydroxylamine may be isolated if the reduction of nitrobenzene is carried out in neutral solution, but not otherwise, for, in the presence of acids, it is rapidly reduced to aniline or converted by an intramolecular rearrangement into para-aminophenol,


(Reduction) (3)


(Rearrangement) (4)

and in alkaline solution it condenses with nitrosobenzene, forming azoxybenzene.

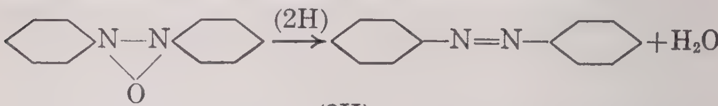
(5)

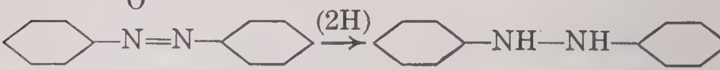


It also undergoes intramolecular oxidation and reduction

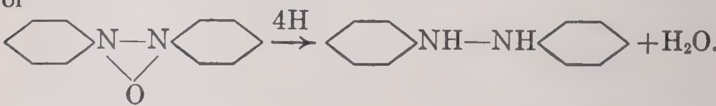
$$2C_6H_5 \cdot NHOH \longrightarrow C_6H_5 \cdot NO + C_6H_5 \cdot NH_2 + H_2O. \quad (6)$$

The next step in the reduction process is the conversion of azoxybenzene to azobenzene and hydrazobenzene.

 (7)

 (8)

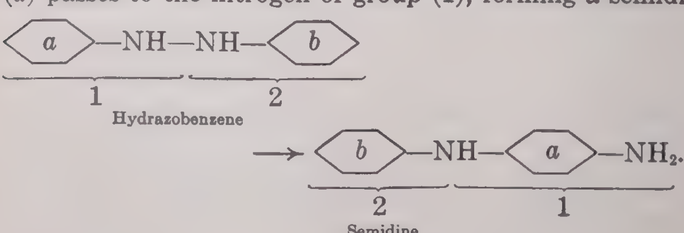
or

 (9)

Much of the azoxy compound is reduced directly to hydrazobenzene, as indicated in the last equation.

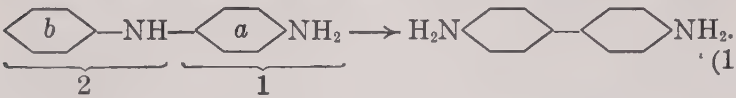
It will be observed that all of these compounds having two nitrogen atoms in the molecule are derived from azoxybenzene. Hence their production depends upon the speed of the condensation between nitrosobenzene and phenylhydroxylamine (equation 5). This proceeds very slowly in the presence of hydrogen ions and rapidly in the presence of hydroxide ions. Hence the azoxy, azo, and hydrazo compounds are not formed in acid reduction but are found among the alkaline reduction products. Unless a proper choice of reducing agent has been made hydrazobenzene does not accumulate in the reaction mixture; for, in acid solution, it either responds to the benzidine change or is reduced to aniline; and in alkaline solution, it is reduced to aniline, or, if the reducing agent is no longer active, it is oxidized by unchanged nitrobenzene to azoxybenzene and azobenzene.

The benzidine change, which is induced by the presence of hydrogen ions, is an example of the Hofmann rearrangement. The group marked (2) migrates from the nitrogen of group (1) to the para position of ring (*a*), and the para hydrogen of ring (*a*) passes to the nitrogen of group (1), forming a semidine:



(10)

This semidine is still a substituted aniline, and group (1) migrates from the nitrogen of group (2) to the para position in ring (*b*), the para hydrogen of ring (*b*) passing to the nitrogen of group (2). The final product of this reaction is benzidine:



(11)

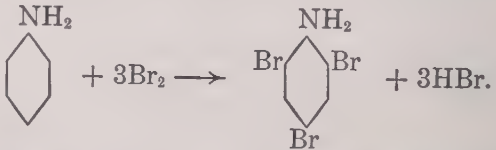
Semidine Benzidine

AROMATIC AMINES

THE PRIMARY AMINES

The aromatic amines are derivatives of ammonia in which hydrogen has been replaced by aryl groups. They are colorless liquids or colorless, crystalline solids, possessing characteristic odors. The primary amines are weak bases: secondary amines are still weaker, forming salts with strong acids only, and these salts are almost completely hydrolyzed in aqueous solution. Tertiary aromatic amines do not form salts with acids.

The substitution of an amino group for hydrogen in the ring renders the remaining hydrogen atoms of the nucleus more reactive. This applies especially to hydrogen in the ortho and para positions. Thus, although bromine water is almost without action on benzene, it rapidly converts aniline into tribromaniline:



Alkyl halides form addition products with primary aromatic amines. Subsequent elimination of halogen acid, by treatment with an alkali, gives rise to mixed aromatic-aliphatic secondary amines:

$$C_6H_5NH_2 + CH_3I \longrightarrow C_6H_5NHCH_3 \cdot HI;$$

$$C_6H_5NHCH_3 \cdot HI + NaOH \longrightarrow C_6H_5NHCH_3 + NaI + H_2O.$$

The primary and secondary amines combine with acids and with acid chlorides, forming amides. Acetanilide is prepared in this way from aniline and acetic acid, or aniline and acetyl chloride. It is a colorless, crystalline compound (m.p. 114.2°, b.p. 303.8°) used in medicine as a febrifuge:

$$C_6H_5 \cdot NH_2 + CH_3 \cdot COOH \longrightarrow CH_3 \cdot CO \cdot NH \cdot C_6H_5 + H_2O;$$

$$C_6H_5 \cdot NH_2 + CH_3 \cdot CO \cdot Cl \longrightarrow CH_3 \cdot CO \cdot NH \cdot C_6H_5 + HCl.$$

Primary aromatic amines react with aldehydes, eliminating water:

$$\underset{\text{Benzaldehyde}}{C_6H_5CH}\boxed{O + H_2}\underset{\text{Aniline}}{N—C_6H_5} \longrightarrow \underset{\text{Benzalaniline}}{C_6H_5CH=N—C_6H_5} + H_2O.$$

They react with the alkali metals, forming salt-like derivatives in which the metal is attached to nitrogen. Potassium, for instance, dissolves rapidly in hot aniline, liberating hydrogen and producing the salts, C_6H_5NHK and $C_6H_5NK_2$.

At low temperatures (0° to 10°) nitrous acid converts primary aromatic amines into diazonium compounds. At higher temperatures the diazonium salts decompose, with an evolution of nitrogen, yielding phenols. The net result at high temperatures is comparable, therefore, to the production of an alcohol from an aliphatic amine:

$$C_6H_5NH_2 + HNO_2 \longrightarrow C_6H_5N_2OH + H_2O;$$
$$C_6H_5N_2OH \longrightarrow C_6H_5OH + N_2.$$

ANILINE

Aniline is a colorless liquid, boiling at 184.4°. It is readily nitrated and sulphonated by concentrated nitric acid and sulphuric acid respectively. Water saturated with the amine at ordinary temperatures contains about three per cent of aniline by weight. Salts of aniline, such as the hydrochloride, $C_6H_5NH_2 \cdot HCl$ and sulphate $(C_6H_5NH_2)_2H_2SO_4$, are crystalline compounds readily soluble in water.

With formaldehyde aniline forms a crystalline condensation product, anhydroformaldehyde-aniline $(C_6H_5 \cdot N : CH_2)_3$, melting at 40°. This may be reduced to methyl aniline. When aniline hydrochloride and formaldehyde are heated in an autoclave, dimethyl aniline is formed, part of the formaldehyde being oxidized to carbon dioxide and part of it being reduced in condensation reactions with aniline (cf. trimethylamine). In a solution of bleaching powder aniline produces a violet color. The reaction mixture contains phenylchloramine, C_6H_5NHCl, and the color is probably due to a condensation product of phenylchloramine with aniline.

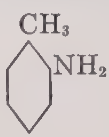
Aniline is prepared commercially from nitrobenzene by reduction with iron and hydrochloric acid. The very dilute hydrochloric acid used dissolves iron, forming ferrous chloride, which is rapidly oxidized by nitrobenzene to ferric chloride

or basic ferric chloride. The ferric salt is hydrolyzed, precipitating ferric hydroxide and liberating hydrochloric acid, which, in turn, brings more iron into solution. A fairly constant hydrogen ion concentration is maintained by the hydrolysis of the ferric salt. This concentration is sufficient to insure further solution of iron, but not sufficient to prevent the precipitation of ferric hydroxide.

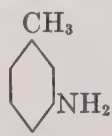
Aniline is manufactured in large quantities to supply the demands of dye factories. It is used also as a laboratory source of halogen-substituted amines and phenols, sulphonic acids, nitroanilines, and homologues of aniline.

Homologues of Aniline

Among the more important compounds derived from aniline by substituting alkyl radicals for hydrogen in the ring are the toluidines and xylidines. There are three toluidines and six xylidines;



o-toluidine
b.p. 199.4°

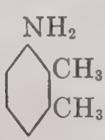


m-toluidine
b.p. 203°

p-toluidine
b.p. 200.5°

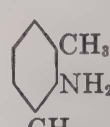
Ortho- and para-toluidine are prepared by reduction of the corresponding nitro-compounds, obtained through direct nitration of toluene. Ortho-toluidine is a liquid, colorless when pure, but red as ordinarily prepared. Para-toluidine is a crystalline solid (m.p. 45°). Meta-toluidine, a liquid, is prepared by reduction of meta-nitrobenzal chloride, or by heating resorcin with the compound of calcium chloride and ammonia ($CaCl_2 \cdot 8NH_3$).

The xylidines are represented by the formulas below. The abbreviations *o*, *m*, *p*, and *v*, refer to ortho, meta, para, and vicinal positions. A vicinal compound is one having a substituent on each of three adjacent carbon atoms in the nucleus.

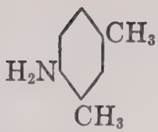


v-*o*-xylidine
1, 2, 3-xylidine
b.p. 223°

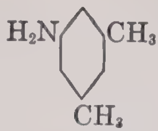
unsym.-*o*-xylidine
1, 2, 4-xylidine
m.p. 49°, b.p. 226°



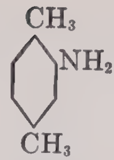
v-*m*-xylidine
1, 3, 2-xylidine
b.p. 216°



unsym.-*m*-xylidine
1, 3, 4-xylidine
b.p. 212°



sym.-*m*-xylidine
1, 3, 5-xylidine
b.p. 220°

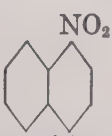


p-xylidine
1, 4, 2-xylidine
m.p. 15°, b.p. 213°

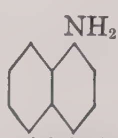
Symmetrical meta-xylidine is prepared from mesitylene by oxidation to mesitylenic acid, from which the corresponding amide is made and subsequently converted into the amine by means of sodium hypobromite.* Commercial xylidine, obtained from crude xylene (*o*, *m*, and *p*, xylene) by nitration and subsequent reduction, contains all of the xylidines except the 1, 3, 5-compound.

Naphthylamines

α-Naphthylamine, $C_{10}H_7NH_2$, crystallizes in the form of needles. It is a colorless compound which has a disagreeable odor. It is very slightly soluble in water but it dissolves readily in alcohol and ether. With acids it forms salts that are soluble in water, and these salts form blue precipitates when treated with oxidizing agents such as ferric chloride, mercuric nitrate, or chromic acid. α-naphthylamine is made from α-nitronaphthalene by reduction with iron and hydrochloric acid.



α-nitronaphthalene
m.p. 61°, b.p. 304°



α-naphthylamine
m.p. 50°, b.p. 301°

β-Naphthylamine, $C_{10}H_7NH_2$, crystallizes in pearly plates. It is odorless and practically insoluble in water. β-naphthol is converted into β-naphthylamine by ammonium sulphite and ammonia at 150° or by heating it with zinc chloride and ammonia.

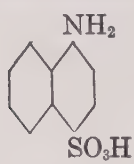
β-naphthol
m.p. 122°, b.p. 286°

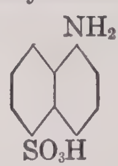
β-naphthylamine
m.p. 112°, b.p. 306°

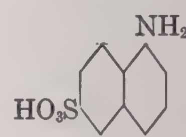
* Haller, Adams, and Wherry, *J. Am. Chem. Soc.*, **42**, 1840 (1920).

This method can be applied with equal success in the preparation of α-naphthylamine. Both of these amines are manufactured in large quantities for use in the dye industry.

The naphthylaminesulphonic acids also are used in large quantities in the preparation of dyes. These derivatives may be made by the action of sulphuric acid on the naphthylamines or by reducing nitronaphthylaminesulphonic acids. The following sulphonic acids are produced when concentrated sulphuric acid acts on α-naphthylamine:

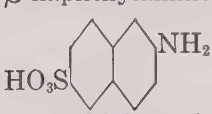




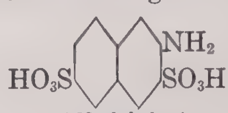


By controlling the time and the temperature of the reaction it is possible to make either of these compounds predominant in the reaction mixture. The first member of this group, 1, 4-naphthylaminesulphonic acid, is commonly called naphthionic acid.

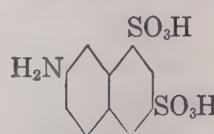
Among the more important sulphonic acid derivatives of β-naphthylamine are the following:



2, 6-Naphthylaminesulphonic acid



2, 3-6-Naphthylamine-disulphonic acid



2, 6-8-Naphthylamine-disulphonic acid

Reference will be made to these compounds in connection with the azo dyes.

Secondary Amines

Diphenylamine, $(C_6H_5)_2NH$ (m.p. 54°, b.p. 310°), a crystalline substance having a pleasant odor, is a typical secondary aromatic amine. It is prepared by heating a mixture of aniline hydrochloride and free aniline, or from brombenzene and potassium anilide:

$$C_6H_5NH_2 \cdot HCl + C_6H_5NH_2 \longrightarrow (C_6H_5)_2NH + NH_4Cl;$$
$$C_6H_5NHK + C_6H_5Br \longrightarrow (C_6H_5)_2NH + KBr.$$

Diphenylamine is oxidized by nitric acid, bromine water, chromic acid, and other oxidizing agents. It yields colored oxidation products — usually blue. Not all of these products have been identified.

Methylaniline, $C_6H_5NHCH_3$ (b.p. 195.5°, sp. gr. 0.987), is a yellow liquid, obtained from aniline by replacing one hydrogen of the amino group by the methyl radical. Direct action of an alkyl halide on aniline gives rise to a mixture of the primary, secondary, and tertiary amines. To obtain the pure secondary amine the following procedure is adopted. Aniline is boiled with glacial acetic acid to form acetanilid, $C_6H_5 \cdot NH \cdot CO \cdot CH_3$, which is converted by methyl iodide into methylacetanilid.

$$C_6H_5 \cdot N\begin{matrix} \diagup H \\ \diagdown COCH_3 \end{matrix} \xrightarrow{CH_3I} C_6H_5 \cdot N\begin{matrix} \diagup CH_3 \\ \diagdown COCH_3 \end{matrix} + HI.$$

This product is hydrolyzed by boiling with a solution of sodium hydroxide, and the methylaniline is obtained by extracting with ether or by distilling with steam.

Tertiary Amines

Triphenylamine, $(C_6H_5)_3N$ (m.p. 127°, b.p. 348°), is a crystalline solid, soluble in acetone and benzene, and practically insoluble in water. It has no basic properties, differing in this respect from the tertiary aliphatic amines. It is prepared by heating diphenylamine and brombenzene with sodium. A sodium derivative of diphenylamine is the first product formed:

$$(C_6H_5)_2NNa + C_6H_5Br \longrightarrow (C_6H_5)_3N + NaBr.$$

Dimethylaniline, $C_6H_5N(CH_3)_2$ (m.p. 2.5°, b.p. 194°), a pale yellow oil having a disagreeable odor, may be prepared from aniline and methyl iodide. An addition product is formed from which hydrogen iodide may be removed by distillation with an alkali. This gives rise to monomethylaniline, and a repetition of the process results in the formation of dimethylaniline:

$$C_6H_5{-}NH_2 + CH_3I \longrightarrow C_6H_5{-}NH_2\begin{matrix} \diagup CH_3 \\ \diagdown I \end{matrix}$$

$$C_6H_5{-}NH_2\begin{matrix} \diagup CH_3 \\ \diagdown I \end{matrix} + NaOH \longrightarrow C_6H_5{-}NH{-}CH_3 + NaI + H_2O$$

$$\begin{matrix} C_6H_5 \diagdown \\ CH_3 \diagup \end{matrix} NH + CH_3I \longrightarrow \begin{matrix} C_6H_5 \diagdown \\ CH_3 \diagup \end{matrix} NH\begin{matrix} \diagup CH_3 \\ \diagdown I \end{matrix}$$

$$\begin{matrix} C_6H_5 \diagdown \\ CH_3 \diagup \end{matrix} NH\begin{matrix} \diagup CH_3 \\ \diagdown I \end{matrix} + NaOH \longrightarrow \begin{matrix} C_6H_5 \diagdown \\ CH_3 \diagup \end{matrix} N{-}CH_3 + NaI + H_2O.$$

Commercially, the amine is manufactured by heating aniline hydrochloride with methyl alcohol. Methyl chloride and water are first formed. The alkyl halide then reacts with aniline, eliminating hydrogen chloride and forming dimethylaniline. The reaction is reversible, and by passing a current of hydrogen chloride through dimethylaniline at 180° the alkyl groups are removed in the form of methyl chloride. A mixture of aniline hydrochloride and methyl alcohol in sealed tubes heated to 250° gives a mixture of aniline, toluidine, xylidine, and mesidine. By proper control of the conditions this method may be used in the preparation of almost any one of the possible products. The mechanism of the reaction is discussed under the Hofmann rearrangement. By this process pentamethylaminobenzene, $C_6(CH_3)_5NH_2$, has been obtained. The yield, however, of any compound containing more than three alkyl radicals attached to the ring is very poor. As a matter of fact, it requires close attention to the details of the process to secure a good yield of mesidine.*

The para-hydrogen atom in dimethylaniline is very reactive. As a result, dimethylaniline forms condensation products with a variety of reagents. The following examples are typical:

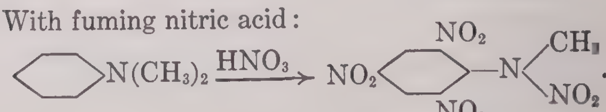
1. With aldehydes:

$$C_6H_5CHO + \begin{matrix} HC_6H_4N(CH_3)_2 \\ HC_6H_4N(CH_3)_2 \end{matrix} \longrightarrow \underset{\text{Leuco-base of malachite green}}{C_6H_5CH{<}\begin{matrix} C_6H_4N(CH_3)_2 \\ C_6H_4N(CH_3)_2 \end{matrix}} + H_2O.$$

2. With phosgene:

$$CO{<}\begin{matrix} Cl \\ Cl \end{matrix} + \begin{matrix} HC_6H_4N(CH_3)_2 \\ HC_6H_4N(CH_3)_2 \end{matrix} \longrightarrow \underset{\text{Michler's ketone}}{CO{<}\begin{matrix} C_6H_4N(CH_3)_2 \\ C_6H_4N(CH_3)_2 \end{matrix}} + 2HCl.$$

3. With fuming nitric acid:



Trinitro-phenylnitroamine

4. With nitrous acid:

Nitroso-dimethylaniline

* Porter and Thurber, *J. Am. Chem. Soc.*, **43**, 1194 (1921).

Nitroso-dimethylaniline formed in this reaction crystallizes in green plates, melting at 85°. Potassium permanganate oxidizes the nitroso to a nitro group.

Secondary amines react with nitrous acid, forming nitroso-amines, the NO group being attached to the nitrogen of the amino group; and primary aromatic amines are diazotized by nitrous acid.

THE DIAZO REACTION

Nitrous acid converts primary aromatic amines into diazonium compounds. The usual procedure for the preparation of these compounds consists in treating a cold, aqueous solution of an amine salt with hydrochloric acid and either amyl nitrite or sodium nitrite. The nitrous acid liberated from the nitrite acts upon the amine salt as follows:

$$C_6H_5NH_2 \cdot HCl + HNO_2 \longrightarrow \begin{array}{c} C_6H_5{-}N{-}Cl \\ \quad\;\; ||| \\ \quad\;\; N \end{array} + 2H_2O.$$

An excess of nitrous acid should be avoided, for it is a fairly active oxidizing agent. Moreover, with some types of compounds — especially secondary and tertiary amines and some phenols — nitroso derivatives are formed. In the manufacture of azo dyes, amines and phenols are used in connection with diazotized primary amines, and in such cases an excess of nitrous acid not only reduces the yield in consequence of undesired reactions, but unnecessarily contaminates the product with other substances, rendering purification difficult and expensive. The sodium nitrite or other source of nitrous acid should be added slowly with constant stirring, until a drop of the mixture produces a blue color on starch-potassium iodide paper.* The structure assigned to the diazonium salt in the above equation is supported by the following considerations:

1. The group $—N_2Cl$ is univalent. It is attached to the ring by one valence bond only, for it is easily replaced by such univalent radicals as OH, CN, and Br.

2. A diazonium compound acts like a salt of a fairly strong base. The group $C_6H_5N_2—$ is comparable to the ammonium group $NH_4—$. The diazonium chloride, like ammonium chloride, is a neutral salt and a highly ionized compound. With

* Free nitrous acid oxidizes iodide ion to free iodine, which imparts a blue color to starch: $2HI + 2HNO_2 \longrightarrow 2H_2O + 2NO + I_2$.

platinum and gold compounds it forms insoluble double salts of the type $(C_6H_5N_2)_2PtCl_6$. Benzene diazonium carbonate, like ammonium carbonate, gives an alkaline reaction in aqueous solution due to hydrolysis. In ammonium hydroxide the hydroxyl group is held by pentavalent nitrogen and the corresponding diazonium structure should indicate a similar relationship between nitrogen and hydroxyl.

But benzenediazonium hydroxide reacts not only with acids but also with bases. Thus we have two types of reactions:

$$C_6H_5N_2OH + HCl \longrightarrow C_6H_5N_2Cl + H_2O,$$
$$C_6H_5N_2OH + KOH \longrightarrow C_6H_5N_2OK + H_2O.$$

Hantzsch explained this anomalous behavior by assuming the existence of tautomeric forms.

$$\begin{array}{c} C_6H_5\text{—}\overset{}{N}\text{—}OH \\ \equiv \\ N \\ \text{Benzenediazonium} \\ \text{hydroxide} \end{array} \rightleftarrows \begin{array}{c} C_6H_5\text{—}N\text{=}N\text{—}OH. \\ \text{Benzenediazo} \\ \text{hydroxide} \end{array}$$

One form contains a pentavalent nitrogen atom and is called a diazonium compound. The other form contains trivalent nitrogen only and is designated a diazo compound. A diazonium hydroxide is a strong base; a diazo hydroxide is a weak acid. Hence in acid solution the diazonium compounds are stable, forming salts of the type $\begin{array}{c}\phi\text{—}N\text{—}X \\ \equiv \\ N\end{array}$, but they change to the diazo form in the presence of bases, forming salts of the type ϕ—N=N—OK. This is a consideration of practical as well as of theoretical importance. Diazo compounds couple with aromatic amines and phenols to form the azo dyes. Hence to produce a dye the reagents should be brought together in alkaline solution.*

The double bond between nitrogen atoms in the diazo compound gives rise to geometrical isomers which are distinguished as *syn* and *anti* compounds.

$$\begin{array}{r} C_6H_5\text{—}N \\ \| \\ KO\text{—}N \end{array} \qquad\qquad \begin{array}{l} C_6H_5\text{—}N \\ \qquad\;\; \| \\ \qquad\;\; N\text{—}OK \end{array}$$

syn Diazo salt *anti* Diazo salt

* In some cases an acid medium is required to hold the reagents in solution. In such cases sodium acetate is usually added to reduce the hydrogen ion concentration to that of an acetic acid solution, for coupling does not occur in solutions of high hydrogen ion concentration.

Anti-diazo compounds are formed in strongly alkaline solutions only. The *syn*-diazo compounds, when warmed, decompose with an evolution of nitrogen. An important exception to this rule, however, is found in the case of the azo dyes. The so-called coupling reactions with amines and phenols produce stable molecules. Both *syn*- and *anti*-diazo compounds are capable of yielding dyes, but the coupling is usually carried out in dilute solutions of bases, and *syn*-compounds are formed. Reduction of an azo dye with stannous or titanous chloride breaks the molecule between the nitrogen atoms, leaving nitrogen attached to each of the aromatic nuclei. This behavior affords further evidence in support of the —N=N— structure of the diazo group.

The *syn*-diazo compounds are less stable and more reactive than the *anti*-compounds. They are hydrolyzed more completely, being salts of a weaker acid. The *syn*-compounds are more easily reduced to hydrazines and more readily oxidized to nitramines; they are more soluble and, in the dry state, more explosive than the corresponding *anti*-diazo bodies. Rapid decomposition with evolution of nitrogen is a characteristic property of the *syn*-series. The *anti*-diazo compounds yield the same decomposition products but the change occurs more slowly and requires a higher temperature, the first step, in all probability, being a rearrangement to the *syn* form.

A *syn*-diazo hydrate has never been isolated, for as soon as liberated from the salt by means of an acid, it either decomposes, yielding a phenol and nitrogen, or it changes to the diazonium form. *Anti*-diazo hydrates have been obtained by treating the corresponding potassium diazotates with acetic acid at low temperatures. They are colorless, crystalline compounds, but they are quite unstable and even at low temperatures in aqueous solution they are rapidly converted into nitrosamines.

Diazonium as well as diazo salts, when dry, are explosive. Detonation is accomplished by percussion or by heat. The important reactions of the diazonium salts are carried out in aqueous solution and it is unnecessary, therefore, to assume the risk of an explosion in dealing with these compounds. Transformations of diazonium salts are used in synthetic work to introduce the following radicals and elements into aromatic nuclei:

1. *Hydroxyl.* When an aqueous solution of a diazonium salt is heated, nitrogen gas escapes and a phenol is formed:

$$C_6H_5N_2Cl + HOH \longrightarrow C_6H_5OH + N_2 + HCl.$$

To obtain a good yield of phenol and to avoid contamination with products formed in side reactions with nitrous acid, it is necessary to make sure (1) that the amine used has been completely diazotized and (2) that no excess of nitrous acid remains in solution. To accomplish the first requirement a slight excess of sodium nitrite is added, and to remove the excess of nitrous acid formed a small quantity of urea is introduced before the mixture is heated. Urea decomposes the nitrous acid according to the equation:

$$CO(NH_2)_2 + 2HNO_2 \longrightarrow CO_2 + 3H_2O + 2N_2.$$

2. *Iodine.* Potassium iodide is added to a solution of the diazonium salt and the mixture is allowed to stand at room temperature several hours. Nitrogen escapes slowly. The mixture is finally heated to complete the reaction.

$$C_6H_5N_2Cl + KI \longrightarrow C_6H_5I + N_2 + KCl.$$

3. *Chlorine, bromine and cyanogen.* The plan outlined in the last paragraph for the introduction of iodine into the ring does not apply to chlorine, bromine or cyanogen. Sandmeyer discovered, however, that in the presence of cuprous chloride, bromide, or cyanide the reaction is analogous to the one in which phenyl iodide is formed.* It is immaterial whether benzenediazonium chloride is heated with cuprous bromide or benzenediazonium bromide is heated with cuprous chloride — phenyl bromide is the product obtained. Chlorine, bromine and the CN group, therefore, may be substituted for the diazo group as indicated below:

$$C_6H_5N_2Cl + CuCl \longrightarrow C_6H_5Cl + N_2 + CuCl;$$
$$C_6H_5N_2Cl + CuBr \longrightarrow C_6H_5Br + N_2 + CuCl;$$
$$C_6H_5N_2Cl + CuCN \longrightarrow C_6H_5CN + N_2 + CuCl.$$

Copper powder or fine filings in connection with KCl, KBr, or KCN may be substituted for the cuprous salts.

4. *Fluorine.* Free fluorine decomposes benzene, forming hydrogen fluoride and carbon. Diazonium salts react with piperidine to form a diazo piperidide;

* Sandmeyer, *Ber.*, **17**; 1633; 2650; (1884). Erdman, *Ann.*, 272; 141 (1872).

$$C_6H_5—N{=}N—N\begin{matrix} \diagup CH_2—CH_2 \diagdown \\ \diagdown CH_2—CH_2 \diagup \end{matrix}CH_2$$

Hydrofluoric acid decomposes this substance, forming fluorbenzene, nitrogen, and piperidine hydrofluoride.

$$C_6H_5—N{=}N—N\begin{matrix} \diagup CH_2—CH_2 \diagdown \\ \diagdown CH_2—CH_2 \diagup \end{matrix}CH_2 + 2\,HF \longrightarrow$$

$$C_6H_5F + N_2 + CH_2\begin{matrix} \diagup CH_2—CH_2 \diagdown \\ \diagdown CH_2—CH_2 \diagup \end{matrix}NH \cdot HF$$

5. *Aryl radicals.* When a dry diazonium salt is dissolved or suspended in benzene, or in any other liquid aromatic hydrocarbon and warmed with aluminum chloride, the diazo group is replaced by an aryl radical:

$$C_6H_5N_2Cl + C_6H_6 \longrightarrow C_6H_5 \cdot C_6H_5 + N_2 + HCl.$$

6. *Hydrogen and alkoxyl.* An alkaline solution of stannous chloride acts upon a diazonium salt, replacing the diazo group by hydrogen:

$$C_6H_5N_2Cl + SnCl_2 + 5KOH$$
$$\longrightarrow C_6H_6 + N_2 + 3KCl + K_2SnO_3 + 2H_2O.$$

In acid solution stannous chloride reduces the compound to a derivative of hydrazine, no nitrogen being evolved.

$$2C_6H_5N_2Cl + 4SnCl_2 + 6HCl \longrightarrow 2C_6H_5NH \cdot NH_2 + 4SnCl_4.$$

Absolute alcohol acts upon a dry diazonium salt, introducing hydrogen, the alcohol being simultaneously oxidized to the corresponding aldehyde:

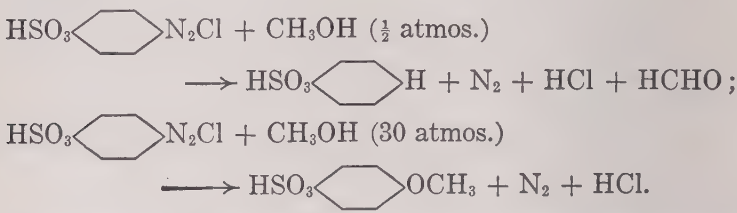
$$C_6H_5N_2Cl + C_2H_5OH \longrightarrow C_6H_6 + N_2 + C_2H_4O + HCl.$$

Alcohol serves also to form an ether:

$$C_6H_5N_2Cl + C_2H_5OH \longrightarrow C_6H_5OC_2H_5 + N_2 + HCl.$$

The temperature and pressure, as well as the nature of the diazonium salt employed, are factors in determining whether the diazo group shall be replaced by hydrogen or by the alkoxyl group. Thus, diazobenzene-sulphonic acid and methyl alcohol under reduced pressure yield benzenesulphonic acid, while

under thirty atmospheres of pressure they form anisol-sulphonic acid only: *



The presence of negative groups in ortho and para positions promotes replacement by hydrogen. Alkyl radicals or other positive groups favor formation of an ether.

HYDRAZINES

Hydrazine, $H_2N—NH_2$ (m.p. 1.4°, b.p. 113°), fumes in moist air, forming a hydrate, and dissolves rapidly in cold water, yielding an alkaline solution. Some of the derivatives of hydrazine are important reagents, and among these phenylhydrazine is preëminent.

Phenylhydrazine, $C_6H_5 \cdot NH \cdot NH_2$ (m.p. 19.6°, b.p. 243°), is a colorless, oily liquid which acquires a red color on standing in contact with air. It is slightly soluble in water and soluble in all proportions in alcohol and ether. It is a basic substance. With acids it forms well-crystallized, soluble salts. It is prepared by reduction of a benzenediazonium salt with an acid solution of stannous chloride, or by treating the diazonium salt with sodium sulphite, zinc dust, and acetic acid. When a sulphite is used the SO_3H group is finally eliminated by boiling with fuming hydrochloric acid. Phenylhydrazine hydrochloride, being almost insoluble in a concentrated solution of hydrochloric acid, is precipitated. This constitutes the usual laboratory procedure.

$$C_6H_5 \cdot N_2 \cdot Cl + Na_2SO_3 \longrightarrow C_6H_5 \cdot N_2 \cdot SO_3Na + NaCl;$$

$$C_6H_5 \cdot N_2 \cdot SO_3Na + Zn + 3\ HC_2H_3O_2 \longrightarrow C_6H_5 \cdot NH \cdot NH \cdot SO_3H + Zn(C_2H_3O_2)_2 + NaC_2H_3O_2;$$

$$C_6H_5 \cdot NH \cdot NH \cdot SO_3H + H_2O \longrightarrow C_6H_5 \cdot NH \cdot NH_2 + H_2SO_4.$$

The structure of phenylhydrazine is established by the following reactions: Methyl aniline is converted by nitrous acid

* Remsen and Palmer, *Am. Chem. J.*, 8, 243 (1886).

into a nitrosamine, which on reduction yields methyl phenylhydrazine.

$$C_6H_5 \cdot N\begin{matrix} \diagup H \\ \diagdown CH_3 \end{matrix} + HNO_2 \longrightarrow C_6H_5 \cdot N\begin{matrix} \diagup NO \\ \diagdown CH_3 \end{matrix} + H_2O;$$

$$C_6H_5 \cdot N\begin{matrix} \diagup NO \\ \diagdown CH_3 \end{matrix} + 4H \longrightarrow C_6H_5 \cdot N\begin{matrix} \diagup NH_2 \\ \diagdown CH_3 \end{matrix} + H_2O.$$

The same product is obtained from phenylhydrazine by treatment with sodium, and subsequent removal of the metal by means of methyl iodide.

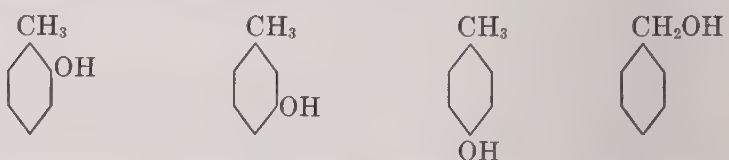
$$C_6H_5 \cdot N\begin{matrix} \diagup NH_2 \\ \diagdown H \end{matrix} + Na \longrightarrow C_6H_5 \cdot N\begin{matrix} \diagup NH_2 \\ \diagdown Na \end{matrix} + \tfrac{1}{2}H_2;$$

$$C_6H_5 \cdot N\begin{matrix} \diagup NH_2 \\ \diagdown Na \end{matrix} + CH_3I \longrightarrow C_6H_5 \cdot N\begin{matrix} \diagup NH_2 \\ \diagdown CH_3 \end{matrix} + NaI.$$

The uses of phenylhydrazine are considered in connection with the general reactions of aldehydes and ketones, and especially with reference to the hydrazones and osazones of the carbohydrates.

PHENOLS

Phenols are compounds derived from aromatic hydrocarbons by substituting hydroxyl for hydrogen in the ring. The aromatic nucleus may be a simple benzene ring, or it may contain condensed rings as found in naphthalene, anthracene, or phenanthrene. The feature that distinguishes a phenol from an aromatic alcohol is the attachment of the hydroxyl group to a carbon atom of the nucleus. It is attached to a side-chain carbon atom in an alcohol. Thus, the formula, C_7H_7OH, represents three phenols and one alcohol:



o-Hydroxy-toluene *m*-Hydroxy-toluene *p*-Hydroxy-toluene Benzyl alcohol

Phenols are classified as monohydric, dihydric, or polyhydric on the basis of the number of hydroxyl groups attached to the nucleus. The termination *ol* is used to denote the presence of alcoholic as well as phenolic hydroxyl. Thus, benzyl alcohol may be called phenyl carbinol and the hydroxy-toluenes are commonly called cresols. The hydroxy derivatives of the xylenes are called xylenols.

Although *phenol* is a general name referring to a class of compounds, it is commonly used to designate a particular compound, C_6H_5OH, also known as carbolic acid.

Preparation. Coal tar is the principal source of ordinary phenol. Some cresols, xylenols, and related compounds occur with it. Phenols are prepared synthetically in several ways:

1. From sulphonic acids by fusion with solid potassium hydroxide. The sulphonic acids are crystalline compounds, formed by the direct action of concentrated sulphuric acid on the aromatic hydrocarbons:

$$\underset{\text{Benzenesulphonic acid}}{C_6H_5SO_3H} + 2KOH \longrightarrow \underset{\text{Phenol}}{C_6H_5OH} + K_2SO_3 + H_2O.$$

2. From aromatic amines through the diazo reaction. Nitrous acid acts upon primary amines, liberating nitrogen and introducing hydroxyl in the place of the NH_2 group. In the aliphatic series this reaction is used to convert amines into alcohols. Aromatic amines yield phenols. The reactions differ in one respect, namely, in the case of the aromatic amines an intermediate product — a diazonium salt — can be isolated; but when heated with water, the diazonium salt yields nitrogen, and a phenol:

$$C_6H_5NH_2 + HCl + HNO_2 \longrightarrow C_6H_5N_2Cl + 2H_2O,$$
$$C_6H_5N_2Cl + HOH \longrightarrow C_6H_5OH + HCl + N_2.$$

Properties. The phenols are colorless, crystalline solids. The lower members have low melting points, characteristic odors, and strong antiseptic properties. They are only slightly soluble in water, the solubilities decreasing rapidly as the molecular weights increase. In alcohol and ether they dissolve readily. They act like weak acids, the hydrogen of the hydroxyl being easily replaced by metals. The resulting phenolates are largely hydrolyzed by water, and completely decomposed by acids. Carbon dioxide in water furnishes a sufficient concentration of hydrogen ions to regenerate phenol from a phenolate. Phenols are insoluble, therefore, in solutions of carbonates, but they dissolve in dilute solutions of sodium or potassium hydroxide.* They ionize to some extent, differing in this respect from the alcohols. Alcohols are non-conductors of electricity. They have no acidic nor basic properties. If they are insoluble in water, they are equally insoluble in dilute alkali. Treatment with metallic sodium or potassium is required to form the alcoholate. The phenyl or any other aryl radical is more negative than an alkyl radical, and consequently an aryl hydroxide (phenol) is more acidic than an alkyl hydroxide (alcohol). The activity of a hydroxyl group depends upon the character of the radical attached to it. Conversely, the nature of the radical is modified by attachment to the hydroxyl or to any other group.

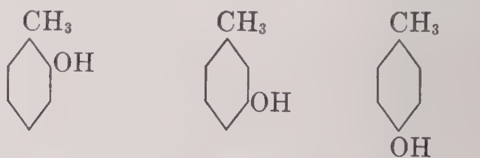
Phenol, C_6H_5OH (m.p. 42°, b.p. 183°), is commonly known as carbolic acid. It dissolves in fifteen times its weight of cold water and forms a crystalline hydrate, $2C_6H_5OH \cdot H_2O$,

* For exceptions see Torrey and Kipper, *J. Am. Chem. Soc.*, **30**, 84 (1908) and Adams, *ibid.*, **41**, 247 (1919).

melting at 16°. At one time phenol was employed quite extensively in surgery, but safer antiseptics such as iodine, alcohol, mercuric chloride, and meta-cresol have rendered its use in this connection obsolete. Phenol is used in the preparation of salicylic acid, phenacetine, and picric acid. It is used also in the manufacture of bakelite and other synthetic plastics.

CRESOLS

According to the structure theory, there should be three cresols, or hydroxytoluenes. Three such compounds are known. They are all obtained from the creosote oil, produced in the distillation of coal tar:

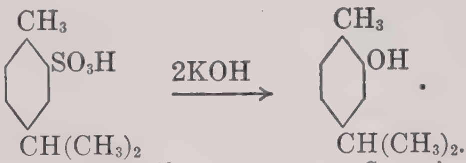


o-Cresol m.p. 30°, b.p. 191° | *m*-Cresol m.p. 4°, b.p. 203° | *p*-Cresol m.p. 36°, b.p. 202°

In physical properties the cresols resemble each other so closely that they cannot be separated and purified by fractional distillation and crystallization. Each may be prepared in a pure state from the corresponding toluidine by means of the diazo reaction. Para-cresol is a decomposition product of some proteins and is found in the form of a sulphonic acid in urine. The cresols are decomposed by hot chromic acid or other vigorous oxidizing agents, unless the hydrogen of the hydroxyl group has been replaced by an alkyl or acyl group. When the alkyl or acyl derivative is oxidized, the methyl group is converted to carboxyl, yielding a hydroxy benzoic acid.

Thymol, a constituent of the essential oils of thyme and mint, is obtained from the plants by extraction with aqueous sodium hydroxide, from which it is precipitated by neutralizing the base. It forms large, colorless crystals (m.p. 50°), only slightly soluble in water (1 : 1100). It is volatile with steam and very soluble in alcohol and ether. Unlike phenol and the cresols, thymol in aqueous solution fails to develop a color in the presence of ferric chloride, and with bromine water only a faint turbidity is produced. Thymol is less active as an antiseptic and much less poisonous than phenol.

Carvacrol (m.p. 1°) is isomeric with thymol, which it resembles in chemical and physical properties. Both of these phenols are derivatives of cymene (*p*-methyl-isopropylbenzene). Carvacrol is obtained by fusing cymene sulphonic acid with potassium hydroxide:



Cymene sulphonic acid — Carvacrol

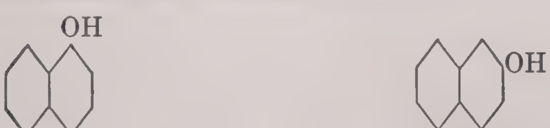
The position of the hydroxyl group is established by the fact that when carvacrol is heated with phosphorus pentoxide, ortho-cresol and propylene are the products formed. In thymol, therefore, the hydroxyl is in a position ortho to the isopropyl group.

NAPHTHOLS

The monohydroxy derivatives of naphthalene are known as naphthols. These compounds are of great importance on account of their use in the manufacture of dyes. They are prepared from the naphthalenesulphonic acids by fusion with potassium hydroxide, or from the naphthylamines by the diazo reaction:

$$C_{10}H_7SO_3H + 2KOH \longrightarrow C_{10}H_7OH + K_2SO_3 + H_2O;$$
$$C_{10}H_7NH_2 + HNO_2 \longrightarrow C_{10}H_7OH + N_2 + H_2O.$$

The naphthols have the following structures:



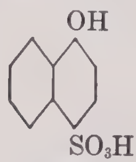
α-Naphthol
m.p. 94°, b.p. 278°

β-Naphthol
m.p. 122°, b.p. 285°

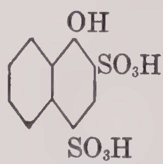
They form colorless, monoclinic crystals, almost insoluble in water, but readily soluble in alcohol, benzene, ether, and chloroform. The naphthols are oxidized by ferric chloride to dinaphthols, $HOC_{10}H_6 \cdot C_{10}H_6OH$. At the same time iron salts of these compounds are formed, giving colored solutions and colored precipitates. α-Naphthol yields a violet, and

β-naphthol a green oxidation product. The hydroxyl groups in the naphthols are very reactive and easily replaced. For example, β-naphthylamine is formed when β-naphthol is heated with the compound of calcium chloride and ammonia.

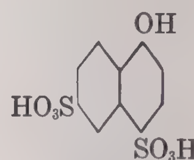
Sulphuric acid acts upon the naphthols, producing substitution products known as naphtholsulphonic acids. Some of these are used in large quantities in the manufacture of dyes. The following derivatives of α-naphthol are valuable representatives of the series



1, 4-Naphthol-sulphonic acid



1, 2-4-Naphthol-disulphonic acid

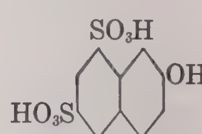


1, 4-6-Naphthol-disulphonic acid

Among the sulphonic acids of technical value derived from β-naphthol are the following:

2, 6-Naphthol-sulphonic acid

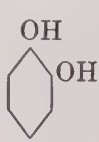
2, 3-6 Naphthol-disulphonic acid



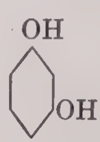
2, 6-8-Naphthol-disulphonic acid

Dihydric Phenols

The three dihydroxy benzenes are the simplest as well as the most important dihydric phenols.



Pyrocatechol
m.p. 104°



Resorcinol
m.p. 119°

Quinol
m.p. 169°

Pyrocatechol is obtained from several natural sources, including sugar beets, the leaves of wild grapes, and many resins. It is prepared synthetically by fusing ortho-phenolsulphonic acid or ortho-bromphenol* with potassium hydroxide. It is

* *Ortho*-chlorphenol, the chief product formed in the direct chlorination of phenol, is cheaper than the corresponding bromine and iodine derivatives. But

easily made from guaiacol, $C_6H_4(OH)(OCH_3)$, by heating with hydriodic acid.

$$C_6H_4\left\langle\begin{matrix} OH\ (1) \\ OCH_3\ (2) \end{matrix}\right. + HI \longrightarrow C_6H_4\left\langle\begin{matrix} OH\ (1) \\ OH\ (2) \end{matrix}\right. + CH_3I$$

Guaiacol is obtained from the creosote oil fraction of beechwood tar. It is a crystalline substance (m.p. 28.5°, b.p. 205°), having a pleasant odor and a sweet taste. Ferric chloride acts upon a dilute alcoholic solution of guaiacol, giving an immediate blue color, which gradually changes to green and finally yellow. When heated with zinc dust, guaiacol yields anisol, $C_6H_5OCH_3$ (m.p. − 37.8°, b.p. 155°).

Pyrocatechol in alkaline solution absorbs oxygen from the air. It precipitates gold, silver, and platinum from their salts. This property makes it useful as a photographic developer, and it is sold for this purpose under the names catechol and pyrocatechin.

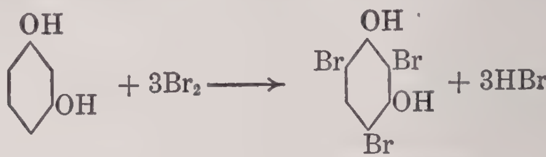
Resorcinol, resorcin, or meta-dihydroxybenzene, is made by heating meta-benzenedisulphonic acid or para-chlorbenzenesulphonic acid, with sodium hydroxide.

Resorcinol is used in the manufacture of fluoresceine and other dyes. When heated with sodium nitrite, it yields the deep blue dye, lacmoid, which turns red in the presence of hydrogen ions and is used as an indicator. Resorcinol forms a violet-colored compound with ferric chloride. Lead acetate does not precipitate this phenol from aqueous solution — a test used to distinguish it from pyrocatechol. It differs from pyrocatechol also in being a much weaker reducing agent. It is, however, active enough as a reducing agent to precipitate cuprous oxide from Fehling's solution and metallic silver from an ammoniacal solution of silver oxide.

Resorcinol crystallizes from benzene in large, colorless needles. It is very soluble in water (147 grams in 100 grams of water

the product formed by fusion of the chlorphenol with alkali is a mixture of *ortho* and *meta* dihydroxy benzenes, and principally the meta compound, resorcinol. It is not uncommon for an ortho or a para disubstitution product of benzene to yield meta dihydroxy benzene when fused with an alkali. The higher the fusion temperature the greater will be the yield of the meta compound. The identification of a compound formed in a reaction involving fusion with a base does not determine the orientation of groups that were present in the molecule before fusion.

at 12.5°). It reacts with bromine water, immediately precipitating tribromresorcinol.

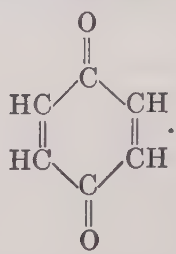


Resorcinol
m.p. 119°

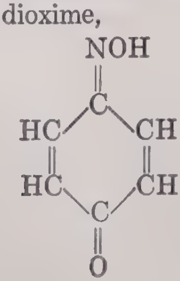
Tribromresorcinol
m.p. 111°

Quinol, hydroquinone, or para-dihydroxybenzene is used extensively as a photographic developer. In reducing power it stands between catechol and resorcin. Oxidizing agents convert it into a yellow, crystalline compound, known as quinone. Hydroquinone crystallizes from water in colorless prisms. Its solubility in water at room temperature is about six parts per hundred.

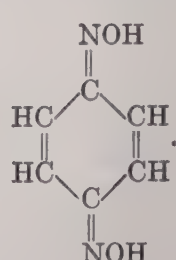
Quinone. The yellow crystalline compound known as quinone is an important oxidation product of hydroquinone, *p*-aminophenol, *p*-sulphanilic acid, and of many other para-disubstitution products of benzene. Its empirical formula is $C_6H_4O_2$ and its genetic relationship to the compounds mentioned above lead to the assumption that its structure is



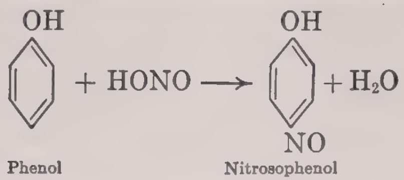
The existence of carbonyl groups in quinone is indicated also by the fact that, with hydroxylamine, quinone yields a monoxime and a dioxime,



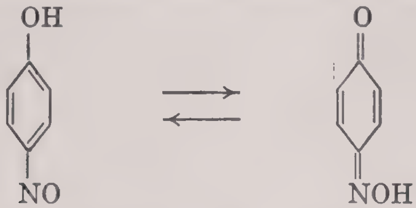
and



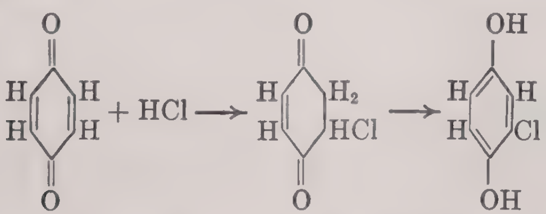
The monoxime is identical with nitrosophenol, a compound formed by the action of nitrous acid on phenol:



A tautomeric equilibrium exists between the two forms.



Rearrangements occur readily in all quinones. For example, with hydrogen chloride, quinone forms an unstable addition product which immediately rearranges to a stable form, as indicated below.

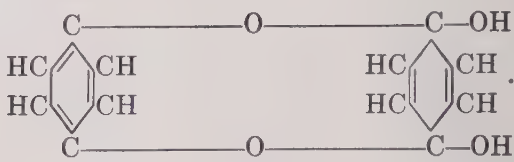


Oxidation of hydroquinone changes the structure of the ring from the benzoid to the quinoid form.

Practically all compounds having the quinoid structure are colored. It has been customary to attribute to this structure the color of quinone. The change in structure, however, is only one of the results attending the oxidation. There may be a more fundamental cause for the display of color. (See theory of color.)

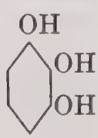
Quinone, $C_6H_4O_2$, forms an addition product with unoxidized molecules of quinol, yielding quinhydrone, $C_6H_4O_2 \cdot C_6H_4(OH)_2$. Ferric chloride carries the oxidation to this stage and the quinhydrone precipitates in the form of red prisms, having a fine, green, metallic luster.

The nature of the tie between quinone and hydroquinone in quinhydrone is not definitely known. The following structure has been proposed:

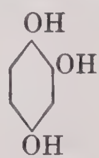


Trihydric Phenols

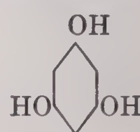
There are three trihydroxy derivatives of benzene:



Pyrogallol
m.p. 132°



Oxyhydroquinone
m.p. 141°



Phloroglucin
m.p. 219°

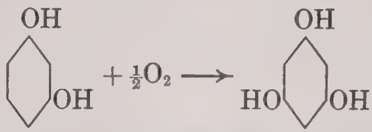
Pyrogallol, pyrogallic acid, or 1, 2, 3-trihydroxybenzene, was first obtained by distilling gallic acid:

$$\underset{\text{Gallic acid}}{C_6H_2(OH)_3COOH\ (1, 2, 3\text{–}5)} \longrightarrow \underset{\text{Pyrogallic acid}}{C_6H_3(OH)_3\ (1, 2, 3)} + CO_2.$$

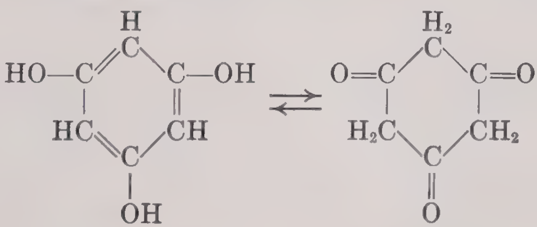
It crystallizes in soft, white leaflets and dissolves in about twice its weight of water. It is a mild poison. An alkaline solution of this phenol absorbs oxygen rapidly, the solution at the same time acquiring a brown or black color. Its principal use is that of an absorbent for oxygen in gas analysis; but it is employed also as a photographic developer.

Oxyhydroquinone, 1, 3, 4-trihydroxybenzene, is prepared from hydroquinone by fusion with sodium hydroxide. The introduction of a hydroxyl group in this manner has been accomplished in many similar cases; the preparation of phloroglucin affords another example. (See also alizarin.) The phenol crystallizes from ether in microscopic plates. It has no unusual properties nor important uses.

Phloroglucin, 1, 3, 5-trihydroxybenzene, was first obtained from phloridizin, a glucoside occurring in the roots and bark of many trees. It is now made by heating resorcin with sodium hydroxide. Oxygen is absorbed from the air by the fused alkaline mixture.



Phloroglucin exhibits the properties of ketones as well as of phenols. It reacts with hydroxylamine, yielding a trioxime, and on the other hand it combines with three molecules of phenylisocyanate, yielding $C_6H_3(O \cdot CO \cdot NH \cdot C_6H_5)_3$, indicating the presence of three hydroxyl groups. The compound exists in two tautomeric forms.



Sodium amalgam acts rapidly upon an aqueous solution of the compound, introducing six hydrogen atoms with the formation of the completely saturated hexahydrophloroglucin.

ALCOHOLS, ALDEHYDES, AND KETONES

ALCOHOLS

The aromatic alcohols are colorless liquids and solids derived from aromatic hydrocarbons by substituting a hydroxyl group for hydrogen in a side chain. Or they may be regarded as derivatives of the aliphatic alcohols in which hydrogen atoms of the alkyl radicals have been replaced by aromatic radicals. Benzyl alcohol, $C_6H_5 \cdot CH_2OH$, is a typical primary alcohol. Diphenylcarbinol, $C_6H_5 \cdot CHOH \cdot C_6H_5$, and triphenylcarbinol, $(C_6H_5)_3COH$, are examples of secondary and tertiary aromatic alcohols.

The primary alcohols may be prepared by reduction of the corresponding aldehydes or by the action of silver hydroxide or potassium hydroxide on compounds having halogen atoms in side chains. Secondary alcohols are usually made from ketones by reduction; and tertiary aromatic alcohols are obtained by oxidizing hydrocarbons having three aryl groups attached to the same carbon atom, or by the action of alkalies on tertiary halogen derivatives of the hydrocarbons. Secondary and tertiary alcohols are readily prepared from aldehydes and ketones, respectively, by means of the Grignard reaction.

Benzyl alcohol, $C_6H_5 \cdot CH_2OH$ (b.p. 106°), is a colorless liquid having a faint pleasant odor. On standing exposed to the air it acquires the odor of almond oil due to the formation of benzaldehyde. In the form of esters of acetic, benzoic, cinnamic, and salicylic acids it occurs in many fragrant flowers and in resins and balsams. It is used extensively in the preparation of artificial perfumes. It is readily prepared by reducing benzaldehyde with sodium amalgam and water or by shaking, for several hours, a mixture of equal volumes of benzaldehyde and a cold saturated aqueous solution of potassium hydroxide. In the latter process half of the benzaldehyde is oxidized to benzoic acid and half is reduced to benzyl alcohol.

$$2C_6H_5 \cdot CHO + KOH \longrightarrow C_6H_5 \cdot COOK + C_6H_5 \cdot CH_2OH$$

Benzyl alcohol is isomeric with the cresols, but differs from them in being less soluble in alkalies, in the ease with which it is oxidized and in the character of the oxidation products.

Phenylethyl alcohol, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot OH$ (b.p. 220°–222°), is made from ethylene oxide and phenylmagnesium bromide.

$$\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>\!O + C_6H_5 \cdot Mg \cdot Br \longrightarrow C_6H_5 \cdot CH_2 \cdot CH_2 \cdot OMgBr$$

The addition product is hydrolyzed by cold water, yielding phenylethyl alcohol, magnesium hydroxide, and magnesium bromide. The alcohol acquires the odor of hyacinths when exposed to air, due to the formation of phenylacetic aldehyde.

ALDEHYDES

The most important aromatic aldehydes are those having the group —CHO attached directly to the benzene ring. Those having the —CHO group attached to carbon in a side chain behave, in all respects, like aliphatic aldehydes. All aromatic aldehydes resemble the aliphatic analogues in their reactions with oxidizing agents, reducing agents, phenylhydrazine, hydroxylamine, and hydrogen cyanide. But those having the —CHO group attached to carbon of the nucleus differ from the aliphatic compounds in their behavior toward ammonia, strong bases, and Fehling's solution. The typical reactions of this group will be considered in connection with benzaldehyde.

The aromatic aldehydes are prepared by the following general methods:

1. Oxidation of a primary aromatic alcohol.

2. Application of heat to a mixture composed of the salt of an aromatic acid and a formate.

$$C_6H_5 \cdot COONa + HCOONa \longrightarrow C_6H_5 \cdot CHO + Na_2CO_3$$

3. Hydrolysis of a compound having the group $—CHCl_2$ attached to the ring.

$$C_6H_5 \cdot CHCl_2 + H_2O \longrightarrow C_6H_5 \cdot CHO + 2HCl$$

4. The action of carbon monoxide and hydrogen chloride on an aromatic hydrocarbon. Dry cuprous chloride and aluminum chloride are used as catalysts (Gattermann's reaction).

Formyl chloride, $H \cdot COCl$, probably is formed through the union of the two gases.

$$C_6H_6 + H \cdot COCl \longrightarrow C_6H_5 \cdot CHO + HCl$$

Benzaldehyde, $C_6H_5 \cdot CHO$ (m.p. $-13.5°$, b.p. $179.1°$), is a colorless oily liquid having the odor of bitter almond oil. It is present in bitter almonds and in cherry kernels in the form of a glucoside called amygdalin. Amygdalin has the empirical formula $C_{20}H_{27}NO_{11}$. On hydrolysis it yields benzaldehyde, glucose, and hydrocyanic acid.

Benzaldehyde is made, commercially, by oxidizing toluene with sixty-five per cent sulphuric acid and powdered manganese dioxide at 40°. It also is made by all of the general methods listed above.

Benzaldehyde reduces an ammoniacal solution of silver hydroxide, but fails to reduce an alkaline solution of cupric ions. Concentrated aqueous solutions of alkalies change benzaldehyde into benzoic acid and benzyl alcohol (p. 282). With ammonia benzaldehyde forms hydrobenzamide $(C_6H_5 \cdot CH)_3N_2$. It reacts with hydroxylamine, yielding benzaldoxime, a compound that exists in two stereoisomeric forms. As obtained in this reaction the oxime is in the form of prismatic crystals which melt at 35°. But, by treatment with hydrochloric acid (which forms a salt of the oxime) and subsequent removal of the acid by means of sodium carbonate, the oxime is obtained in the form of slender needles melting at 128°. We have here an example of geometrical isomerism. The two oximes have the formulas,

$$\begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \qquad \| \\ \qquad N\text{—}OH \end{array} \qquad \text{and} \qquad \begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \qquad \| \\ HO\text{—}N \end{array}$$

Benz*syn*aldoxime m.p. 128° — Benz*anti*aldoxime m.p. 35°

The *syn*- compound, that is, the one having the hydrogen and hydroxyl on the same side of the molecule, loses water when heated with acetic anhydride. Phenylcyanide is thus formed. The *anti*- compound fails to respond in this way but forms an acetyl derivative of the oxime.

Benzaldehyde combines with aniline, forming benzylideneaniline, $C_6H_5 \cdot CH : N \cdot C_6H_5$ (m.p. 42°). With dimethyl aniline it forms tetramethyldiaminotriphenyl methane.

When warmed with a solution of potassium cyanide, benzaldehyde is converted into benzoin.

$$2C_6H_5 \cdot CHO \longrightarrow \underset{\substack{\text{Benzoin} \\ \text{m.p. } 137°}}{C_6H_5 \cdot CHOH \cdot CO \cdot C_6H_5}$$

This is known as the benzoin condensation.*

KETONES

The aromatic ketones are prepared by the following methods:

1. The action of an acid chloride on an aromatic hydrocarbon in the presence of aluminum chloride.
2. The distillation of a salt or a mixture of salts of aromatic acids.
3. The oxidation of an aromatic secondary alcohol.

Acetophenone, $CH_3 \cdot CO \cdot C_6H_5$ (m.p. 20°, b.p. 200°), is a typical example of the mixed aliphatic-aromatic ketones. It is a crystalline compound having an agreeable odor. It is used in medicine as a soporific and dispensed under the name of hypnone. It is usually made by treating a mixture of benzene and acetyl chloride with dry aluminum chloride.

$$CH_3 \cdot COCl + C_6H_6 \longrightarrow CH_3 \cdot CO \cdot C_6H_5 + HCl$$

A special method for making acetophenone by passing the mixed vapors of acetic and benzoic acids over thorium oxide at 450° is also practical.

Benzophenone, $C_6H_5 \cdot CO \cdot C_6H_5$ (m.p. 48.5°, b.p. 306.1°), a colorless crystalline compound, is practically insoluble in water but fairly soluble in alcohol and in ether. It dissolves in sulphuric acid and precipitates unchanged when the acid is diluted with water. It is readily nitrated and chlorinated.

Benzophenone may be prepared by heating benzoyl chloride and benzene with aluminum chloride or by distilling a salt of benzoic acid.

$$\underset{\text{Calcium benzoate}}{(C_6H_5 \cdot COO)_2Ca} \longrightarrow \underset{\text{Benzophenone}}{C_6H_5 \cdot CO \cdot C_6H_5} + CaCO_3$$

Sodium amalgam, or zinc and potassium hydroxide, may be used on alcoholic solutions of benzophenone for the preparation of benzhydrol, $C_6H_5 \cdot CHOH \cdot C_6H_5$, a secondary alcohol

* Lachman, *J. Am. Chem. Soc.*, **45**, 1529 (1923). Staudinger, *Ber.*, **46**, 3535 (1913). Liebig and Wohler, *Ann.*, **3**, 266 (1832).

which crystallizes in needles melting at 68°. Red phosphorus and hydrogen iodide reduce the ketone to the corresponding hydrocarbon, diphenylmethane.

When a saturated solution of benzophenone in fifty per cent alcohol is exposed to the ultraviolet rays of a mercury vapor arc lamp, the ketone is reduced by the alcohol to benzpinacol. The reduction product is less soluble than the ketone and it precipitates in a very pure state.*

$$2C_6H_5{-}CO{-}C_6H_5 + C_2H_5OH \longrightarrow \begin{array}{c} OH \\ | \\ C_6H_5{-}C{-}C_6H_5 \\ | \\ C_6H_5{-}C{-}C_6H_5 \\ | \\ OH \\ \text{Benzpinacol} \\ \text{m.p. } 186° \end{array} + CH_3{\cdot}CHO$$

Benzophenone exists in two crystalline forms, one melting at 27° and the other at 48.5°. The low melting form is unstable. It gradually changes into the stable modification. But the process is not reversible. The transition temperature is evidently above 27°.†

Like other ketones, benzophenone reacts with phosphorus pentachloride, hydroxylamine, phenylhydrazine, and the alkyl and aryl magnesium halides. Some of these reactions are outlined in later chapters.

* Porter, Ramsperger, and Steel, *J. Am. Chem. Soc.*, 45, 1827 (1923).

† Compare this case with the reversible transition of rhombic to monoclinic sulphur at 96°.

AROMATIC ACIDS

The principal methods for preparing the aromatic acids are the following:

1. Oxidation of aromatic hydrocarbons having one or more side chains.
2. Oxidation of aromatic alcohols and aldehydes.
3. Hydrolysis of nitriles.

Benzoic acid, $C_6H_5 \cdot COOH$ (m.p. 121.4°, b.p. 250°), is a colorless crystalline compound which occurs in many resins and particularly in gum benzoin. It has been isolated from cranberries and some other fruits. It is found in coal tar also. On a commercial scale it is made by chlorinating hot toluene, then hydrolyzing the resulting benzotrichloride by boiling with water and calcium hydroxide.

$$C_6H_5 \cdot CH_3 + 3Cl_2 \longrightarrow C_6H_5 \cdot CCl_3 + 3HCl$$
$$C_6H_5 \cdot CCl_3 + 2H_2O \longrightarrow C_6H_5 \cdot COOH + 3HCl$$

Benzoic acid is only slightly soluble in cold water (1 : 144 at 20°). It is twenty times as soluble in boiling water. It is volatile with steam and is usually purified by distillation with steam. It can be reduced to benzyl alcohol by sodium amalgam and water. Hydrogen iodide converts it into toluene. When heated with lime, it yields benzene and carbon dioxide.

The sodium salt of benzoic acid has mild antiseptic properties. It has been used extensively as a preservative for foods. The pure food law permits this practice if the amount of sodium benzoate used is specified on the label of the container.

DERIVATIVES OF BENZOIC ACID

Benzoyl chloride, $C_6H_5 \cdot COCl$ (b.p. 194°), is a colorless liquid with a disagreeable odor. Its fumes have an irritating effect upon the eyes, causing tears.

The benzoyl group, $C_6H_5CO—$, may be substituted for hydrogen in a hydroxyl or an amino group by mixing an alcohol,

phenol, or amine with benzoyl chloride (Schotten-Baumann reaction).

Benzoyl chloride is made by treating benzoic acid with phosphorus pentachloride or by the action of chlorine on benzaldehyde.

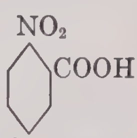
$$C_6H_5 \cdot COOH + PCl_5 \longrightarrow C_6H_5 \cdot COCl + POCl_3 + HCl$$
$$C_6H_5 \cdot CHO + Cl_2 \longrightarrow C_6H_5 \cdot COCl + HCl$$

Benzamide, $C_6H_5CONH_2$ (m.p. 130°), is obtained from benzoyl chloride through the action of ammonia. It is soluble in hot water, but precipitates in the form of colorless plates when the solution is cooled. It acts like a weak acid, dissolving readily in alkaline solutions with the formation of salts of the type $C_6H_5 \cdot CONHM$ (M = metal). When benzamide is heated with phosphorus pentoxide, benzonitrile is formed.

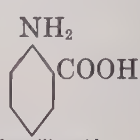
$$C_6H_5 \cdot CONH_2 \longrightarrow C_6H_5 \cdot CN + H_2O$$

Nitrobenzoic acids. Meta-nitrobenzoic acid is prepared by the direct action of nitric acid on benzoic acid. It crystallizes in plates melting at 141°. The ortho- and para-nitrobenzoic acids are made from the corresponding nitrotoluenes by oxidation with potassium permanganate. Ortho-nitrobenzoic acid has a sweet taste. The meta- and para-compounds are bitter.

Anthranilic acid or ortho-aminobenzoic acid is obtained from ortho-nitrobenzoic acid by reduction with tin and hydrochloric acid.

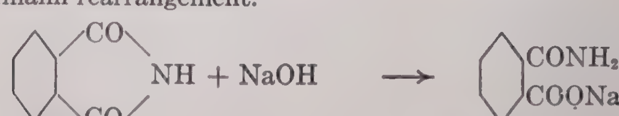


o-Nitrobenzoic acid
m.p. 148°



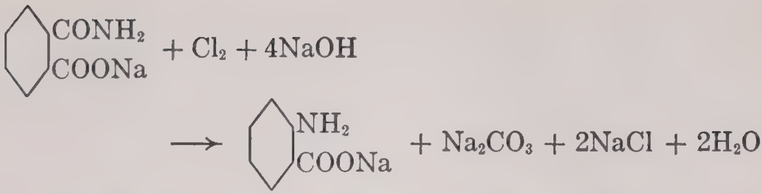
Anthranilic acid
m.p. 145°

On a commercial scale it is made from phthalimide by hydrolysis to phthalamic acid and subsequent treatment with chlorine and sodium hydroxide. This method is an application of the Hofmann rearrangement.

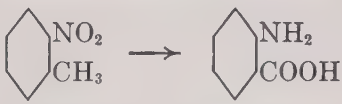


Phthalimide

Salt of phthalamic acid

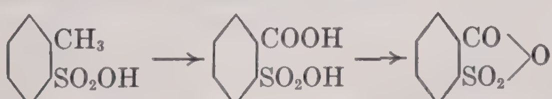


Another interesting synthesis of anthranilic acid is accomplished by boiling *o*-nitrotoluene with a solution of potassium hydroxide. An intramolecular oxidation and reduction occurs.



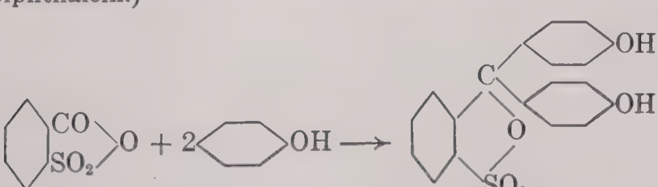
Anthranilic acid is soluble in water and in alcohol. It has a sweet taste. Its methyl ester has an agreeable odor resembling that of orange blossoms. It is used in the manufacture of perfumes.

Sulphobenzoic acid. Ortho-sulphobenzoic acid is made by oxidizing *o*-toluenesulphonic acid. It is a colorless crystalline compound melting at 130°. At higher temperatures it gradually loses water and forms an anhydride.



o-Toluenesulphonic acid *o*-Sulphobenzoic acid Sulphobenzoic anhydride

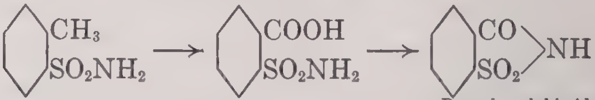
The anhydride combines with phenol when a mixture of the two reagents is warmed with zinc chloride. The resulting compound, phenolsulphophthalein, is a valuable indicator in the determination of hydrogen ion concentrations. (See also phenolphthalein.)



Phenol sulphophthalein

A derivative of sulphobenzoic acid, known as saccharin, is manufactured in large amounts. It is approximately five hundred times as sweet as cane sugar, and although it has no

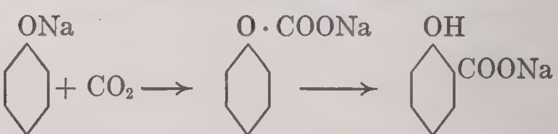
dietetic value, it is used extensively as a substitute for sugar. It is made by oxidizing the amide of *o*-toluenesulphonic acid with potassium permanganate. The amide of *o*-sulphobenzoic acid is first produced, but when heated, it yields a molecule of water and benzoic sulphimide or saccharin.



Benzoic sulphimide

Salicylic acid or *o*-hydroxybenzoic acid, $HO \cdot C_6H_4 \cdot COOH$, occurs in nature as a constituent of the glucoside, salicin, in the bark and leaves of the willow. The methyl ester of salicylic acid is present in oil of wintergreen. The ester is made in large quantities for use in the manufacture of artificial flavors and perfumes.

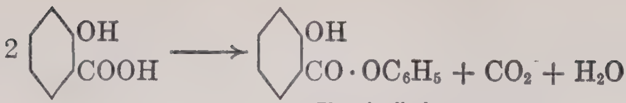
Salicylic acid is made commercially by heating sodium phenolate with carbon dioxide under ten atmospheres of pressure. At 100° the carbon dioxide is absorbed, forming sodium phenyl carbonate. At 120°–140° this product undergoes an intramolecular rearrangement, yielding sodium salicylate.



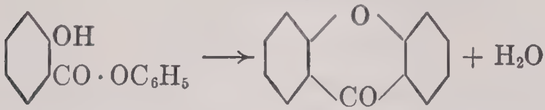
It may be prepared also by fusing ortho-sulphobenzoic acid with potassium hydroxide or by the action of nitrous acid on anthranilic acid.

Salicylic acid is soluble in hot water. It crystallizes from water in colorless needles, melting at 159°. With ferric chloride, in neutral solution, it acquires a violet color. This color test distinguishes *ortho*-hydroxy benzoic acid from the corresponding *meta* and *para* compounds. Another characteristic reaction of the *ortho* compound is its reduction by sodium, in boiling amyl alcohol, with the production of pimelic acid, $COOH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot COOH$. Some other *ortho*-hydroxy acids of the aromatic series are reduced in the same way to homologues of pimelic acid.

When dry salicylic acid is heated with lime, it yields phenol and carbon dioxide. When heated alone, it yields phenyl salicylate, carbon dioxide, and xanthone.

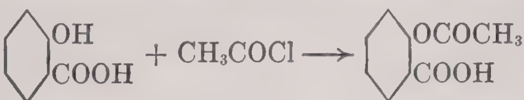


Phenyl salicylate



Xanthone

Phenyl salicylate is used in medicine and is dispensed under the name of *salol.* It is usually prepared by heating a mixture of sodium salicylate, sodium phenolate, and phosphorus oxychloride. Acetylsalicylic acid, commonly called *aspirin,* is another derivative of hydroxybenzoic acid that has therapeutic value. It is made by heating salicylic acid with acetyl chloride.



Acetylsalicylic acid

Other derivatives are used in the manufacture of dyes and in the synthesis of perfumes. The annual production of salicylic acid in the United States exceeds 3000 tons.

Cinnamic acid, $C_6H_5 \cdot CH:CH \cdot COOH$, is an example of the type of aromatic acids having the carboxyl group in an unsaturated side chain.

Benzaldehyde reacts with an acetate in the presence of acetic anhydride, forming an addition product which loses a molecule of water and yields cinnamic acid. (See Perkin's reaction.)

$$C_6H_5 \cdot CHO + CH_3 \cdot COONa \longrightarrow C_6H_5 \cdot CHOH \cdot CH_2 \cdot COONa$$

$$C_6H_5 \cdot CHOH \cdot CH_2 \cdot COONa \longrightarrow \underset{\text{Sodium cinnamate}}{C_6H_5 \cdot CH:CH \cdot COONa} + H_2O$$

Two stereochemical structures are possible for the acid, namely,

$$\begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \| \\ H\text{—}C\text{—}COOH \\ \textit{Trans} \end{array} \qquad \text{and} \qquad \begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \| \\ HOOC\text{—}C\text{—}H \\ \textit{Cis} \end{array}$$

Four modifications of cinnamic acid are known. Ordinary cinnamic acid (m.p. 134°) has the *trans* structure. The *cis*

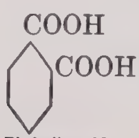
formula has to be assigned to the other three acids — allocinnamic acid (m.p. 68°), and two isocinnamic acids, one melting at 58° and the other at 42° — for these three forms are all obtained by reduction of phenylpropiolic acid,

$$C_6H_5—C{\equiv}C—COOH.$$

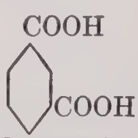
This constitutes an interesting case of trimorphism. The compound has a definite and constant chemical structure, but it crystallizes in three different forms. It can be made to crystallize in either of the three forms by inoculating the molten mass with a small crystal of the desired kind.

DICARBOXYLIC ACIDS

The three benzene dicarboxylic acids are the simplest and most important dibasic aromatic acids. They are known as *ortho*, *meta*, and *para* phthalic acids.



ortho-Phthalic acid
(phthalic)



meta-Phthalic acid
(isophthalic)

para-Phthalic acid
(terephthalic)

They may be prepared from the corresponding xylenes by boiling with dilute nitric acid or from the toluic acids by oxidation with alkaline permanganate solution. The ortho compound, ordinary phthalic acid, is manufactured commercially by oxidizing naphthalene with sulphuric acid. Mercury is used as a catalyst. It crystallizes in colorless prisms, melting between 184° and 213°. Failure to melt sharply at a definite temperature is due to its gradual loss of water with the production of an anhydride. When either of the phthalic acids is mixed with lime and heated gently, the first product formed is benzoic acid. At a higher temperature the benzoic acid is converted into benzene. Carbon dioxide is evolved in each step.

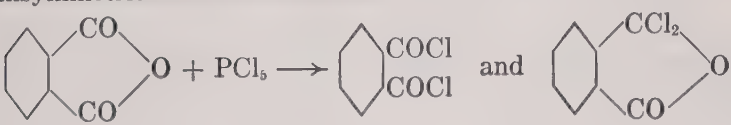
Phthalic anhydride is made by distilling phthalic acid or by passing a mixture of air and naphthalene vapor over hot vanadium oxide. It is used in the manufacture of phenolphthalein, the phthalein dyes, anthraquinone, and phthalimide. Phthalimide (m.p. 229°) is used in the preparation of amines and amino

acids. It is made by passing ammonia over molten phthalic anhydride.

Phthalic anhydride Phthalimide

Phthalic anhydride crystallizes in long, slender needles melting at 131°. It takes up water very slowly, but dissolves rapidly in an alkaline solution, forming a salt of phthalic acid.

Phosphorus pentachloride acts upon phthalic acid, forming phthalyl chloride. This compound exists in two forms. One form, having a symmetrical structure, melts at 16°. The unsymmetrical chloride melts at 88°–89°

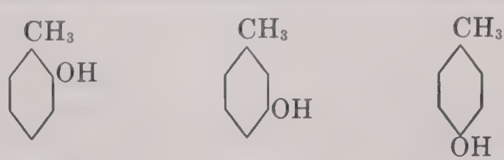


Orientation

Any systematic procedure which enables us to assign definite positions to atoms or groups within a molecule constitutes a method of determining orientation. With reference to side chains or other substituents in cyclic compounds, two general methods of determining orientation have been developed.

THE RELATIVE METHOD

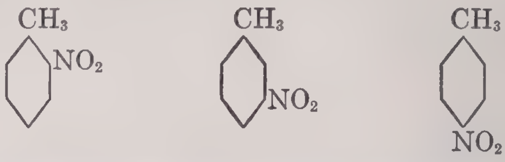
A new derivative of benzene can usually be converted into a derivative of known structure by reactions which do not change the relative positions of the substituents, and thereby the structure of the new compound is revealed. For example, let us assume that the structures of the three cresols are known:



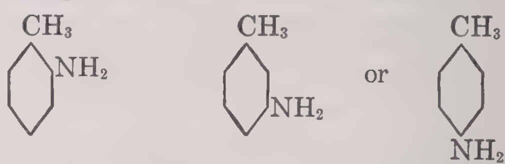
Ortho-cresol m.p. 30° *Meta*-cresol m.p. 4° *Para*-cresol m.p. 36°

Three mononitro derivatives of toluene are known. One of them melts at 52°. Suppose the problem before us is that of deciding

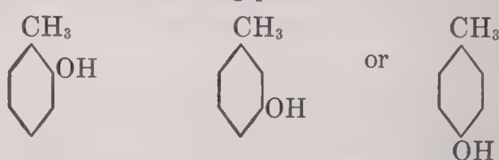
which of the following possible structures should be assigned to this particular compound:



By reducing the nitro-compound with tin and hydrochloric acid the corresponding amino derivative is obtained:



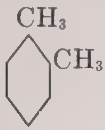
The amino group is readily replaced by hydroxyl through the diazo reaction and the resulting phenol is:

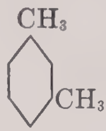


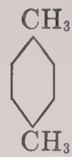
From the nitro-compound melting at 52° we obtain a phenol (in this case a cresol), melting at 36°. Our compound is, therefore, *para*-nitrotoluene. Similarly, a nitrotoluene melting at 16° yields a cresol melting at 4° and is therefore a *meta*-nitro-compound, while a nitrotoluene melting at −10.5° yields a cresol which melts at 30°, and we assign to it the *ortho* structure. The *ortho*-nitrotoluene, on reduction, yields a toluidine which boils at 199°. *Meta*-nitrotoluene, when reduced, yields *meta*-toluidine, boiling at 203°, and the *para*-compound gives rise to crystalline solid toluidine, melting at 43° and boiling at 200°. From this point on, the toluidines and the nitro-compounds, as well as the cresols, may serve as known structures, to which new compounds may be referred. The relative method is based upon the assumption that a few structures for reference have been definitely established by other means. It is necessary, therefore, to determine the structures of a limited number of compounds without reference to known derivatives. The most successful plan for accomplishing this is Korner's absolute method of orientation.

THE ABSOLUTE METHOD

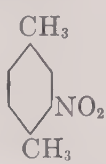
There are three xylenes:



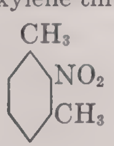


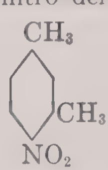


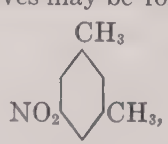
One of them melts at $-54°$, one at $-28°$, and the other at $15°$. The corresponding boiling points are $139°$, $142°$, and $138°$. Which of the three formulas should be assigned to the compound that melts at $-54°$ and which corresponds to each of the other sets of physical properties? On treatment with nitric acid, the xylene melting at $-28°$ yields two different mononitro-derivatives. It is possible to obtain three isomeric mononitroxylenes from the one that melts at $-54°$, but only one mononitroxylene is formed from the compound melting at $15°$. Now, *para*-xylene can form only one mono-substitution product, for the four hydrogen atoms remaining in the ring are similarly located in a symmetrical molecule. The nitro group must become attached to the ring, *ortho* to one methyl group and *meta* to the other:



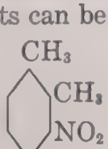
From *meta*-xylene three mononitro-derivatives may be formed:

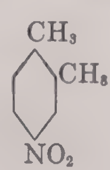






and from the *ortho* compound two and only two mono-substitution products can be prepared:





Hence the xylenes melting at $-54°$, $-28°$, and $15°$ are *meta, ortho,* and *para* compounds respectively.

EQUIVALENCE OF THE HYDROGEN ATOMS IN BENZENE

The fact that there are no isomeric monosubstitution products of benzene is good evidence that the molecule is symmetrical, the hydrogen atoms occupying exactly similar positions. A more rigid proof is based upon the work of Ladenburg and Nolting. Nitrobenzene is converted into aniline by reduction, and the amino group of aniline is replaced by bromine through the diazo reaction. By means of sodium and methyl bromide this product is changed to toluene. Designating the six positions of hydrogen by letters, we have for benzene

$$C_6\overset{a}{H}\ \overset{b}{H}\ \overset{c}{H}\ \overset{d}{H}\ \overset{e}{H}\ \overset{f}{H}.$$

Assigning position *a* to the nitro group in nitrobenzene, we have

$$\underset{\text{Nitrobenzene}}{C_6H_5\overset{a}{N}O_2} \longrightarrow \underset{\text{Aniline}}{C_6H_5\overset{a}{N}H_2} \longrightarrow \underset{\text{Brombenzene}}{C_6H_5\overset{a}{Br}} \longrightarrow \underset{\text{Toluene}}{C_6H_5(\overset{a}{C}H_3)}.$$

When toluene is treated with concentrated nitric acid, three mononitrotoluenes are formed. Let the positions of the nitro-groups in the three compounds be designated by the letters *b, c,* and *d*. We have then $C_6H_4\overset{a}{C}H_3\overset{b}{N}O_2$, $C_6H_4\overset{a}{C}H_3\overset{c}{N}O_2$, and $C_6H_4\overset{a}{C}H_3\overset{d}{N}O_2$. Chromic acid oxidizes these nitrotoluenes to nitrobenzoic acids, $C_6H_4CO\overset{a}{O}H\ \overset{b}{N}O_2$, $C_6H_4CO\overset{a}{O}H\ \overset{c}{N}O_2$, and $C_6H_4CO\overset{a}{O}H\ \overset{d}{N}O_2$. Distillation with lime destroys the carboxyl group, leaving hydrogen in its place, and we obtain $C_6H_4\overset{a}{H}\ \overset{b}{N}O_2$, $C_6H_4\overset{a}{H}\ \overset{c}{N}O_2$, and $C_6H_4\overset{a}{H}\ \overset{d}{N}O_2$. These products are identical with each other and with the original nitrobenzene in which the nitro group was in position *a*. Hence positions *a, b, c,* and *d* are identically alike. Begin now with ortho-toluidine, a compound having the methyl and amino groups occupying two of the four positions already proved to be alike. We may call these positions *a* and *b*, $C_6H_4\ \overset{a}{C}H_3\ \overset{b}{N}H_2$. The amino group may be protected (that is, rendered inactive) by treatment with acetyl chloride, yielding $C_6H_4\ \overset{a}{C}H_3\ NHC\overset{b}{O}CH_3$. This product reacts with concentrated nitric acid, producing four

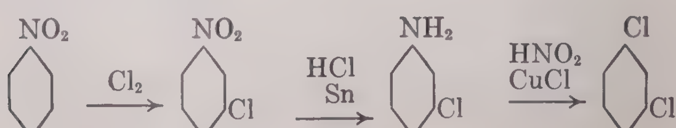
different mononitro derivatives. Since the *a* and *b* positions are occupied by other groups the nitro groups must be at the four remaining positions, *c*, *d*, *e*, and *f*. After nitration the amino group may be restored by hydrolysis of the acetyl derivative and we have $C_6H_3\ \overset{a}{C}H_3\ \overset{b}{N}H_2\ \overset{c}{N}O_2$, $C_6H_3\overset{a}{C}H_3\overset{b}{N}H_2\overset{d}{N}O_2$, $C_6H_3\overset{a}{C}H_3\overset{b}{N}H_2\overset{e}{N}O_2$, and $C_6H_3\overset{a}{C}H_3\overset{b}{N}H_2\overset{f}{N}O_2$. The amino group may be replaced by hydrogen by means of the diazo reaction, leaving four nitrotoluenes $C_6H_4\overset{a}{C}H_3N\overset{c}{O}_2$, $C_6H_4\overset{a}{C}H_3\overset{d}{N}O_2$, $C_6H_4\overset{a}{C}H_3\overset{e}{N}O_2$ and $C_6H_4\overset{a}{C}H_3\overset{f}{N}O_2$. These four structures correspond to only three different compounds, and each of these three compounds is identical with one of the three nitrotoluenes described above.

STERIC INFLUENCES OF SUBSTITUENTS

Orientation. When a monosubstitution product of benzene is converted into a disubstitution product, there exists the possibility of forming either an ortho, meta, or para compound, or a mixture of these. The three derivatives are not formed in equal quantities. The product is almost exclusively the meta compound, or else it is a mixture of the ortho and para compounds. Whether the second substituent shall enter the meta position or shall be distributed between the ortho and para positions depends upon the group already present in the ring. Thus, for example, when chlorbenzene is nitrated, we obtain chiefly para-chlornitrobenzene, but also some of the ortho compound. If, on the other hand, we chlorinate nitrobenzene, we obtain, almost exclusively, meta-chlornitrobenzene. The groups, NH_2, CH_3, C_2H_5, OH, Cl, Br, I, CH_2COOH, and C_6H_5 are among those which, if already in the ring, direct the entering substituent to ortho and para positions. The groups that direct to the meta position are NO_2, SO_3H, CN, CHO, COOH, and COOR.

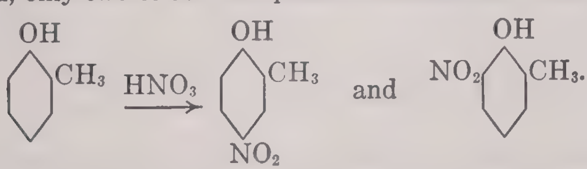
The groups CCl_3 and CF_3 direct chlorine and bromine to *ortho* and *para* positions, but nitration of benzotrichloride, $C_6H_5CCl_3$, or of benzotrifluoride occurs in the *meta* position. Other irregular nitration processes have been observed. In the presence of a large amount of concentrated sulphuric acid aniline and nitric acid yield *meta*-nitroaniline.

Indirect methods are used to synthesize derivatives having elements of the first group meta to each other, or elements of the second group in ortho or para positions. For instance, meta-dichlorbenzene may be made by chlorinating nitrobenzene, then reducing the nitro-group, diazotizing, and warming with cuprous chloride:

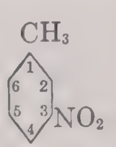


The introduction of a third substituent into the ring brings into play the orienting influences of both groups already present. Suppose, for example, that we brominate sulphanilic acid, H_2NSO_3H. Both groups direct the entering bromine atom to the same place, namely, ortho to the amino radical, but the bromination of *p*-chloraniline H_2NCl, involves the introduction of the entering bromine meta to either chlorine or the amino group, in opposition to the influence of a radical of the first list. In this case the bromine enters the ring *ortho* to the amino group, indicating that the influence of the NH_2 group is greater than that of chlorine. In *para*-aminophenol bromination occurs *ortho* to the hydroxyl group. Attempts have been made to list the principal radicals in the order of their power to determine the orientation of substituents in the benzene nucleus. But the place assigned to a group in such a series varies as determined by different types of reactions.*

Differences in power to direct the entering element means, merely, that one group induces substitution with greater velocity than does some other group. The difference in velocity may be great enough to prevent entirely the formation of some of the possible isomers. When ortho-cresol is chlorinated or nitrated, only two of the four possible isomers are formed:



A group directing to the meta position is unable to force the entering substituent into a position that is also meta to one of the groups included in the first list given above. Thus, although the nitro-group is very effective among those governing the meta position, substitution in meta-nitrotoluene never occurs in position 5:



* For a tabulation of experimental results see A. F. Holleman, Die Direkte Einfuhrung von Substituenten in den Benzolkern.

Many attempts have been made to reduce the empirical rules of substitution reactions to a definite system. Some of the more fruitful efforts in this direction may be summarized briefly.

Crum Brown-Gibson rule.* If the radical already present forms a compound with hydrogen which can be readily and directly oxidized to a corresponding hydroxyl derivative, the entering substituent will take the meta position; otherwise, it will enter the ortho-para positions. Thus, CHO forms the compound $H \cdot CHO$ which is oxidized to $H \cdot COOH$ without the formation of an intermediate product. But NH_2, by addition of hydrogen, yields ammonia, HNH_2, which cannot be converted in one step into NH_2OH. The former, therefore, governs the meta and the latter the ortho-para positions.

Flürscheim's theory. Adopting Werner's theory of valence, Flürscheim † assumes that the affinity of any free atom is evenly distributed over its surface, but when this affinity or part of it is used in holding other atoms, it may become concentrated in small areas, the distribution being dependent upon the environment and the nature of the atoms attached. An element or group that has a strong affinity for carbon, such as Cl, OH, or NH_2, becomes firmly attached to carbon in the benzene ring, pulling toward itself a large share of the total disposable surface attraction. This weakens the union between the carbon atom involved and the two ortho carbon atoms, leaving on the ortho carbon atoms a surplus of affinity for the attachment of the entering substituent. A nitro group, on the other hand, is supposed to be loosely bound to carbon, using less of the disposable affinity of the carbon atom. The union between this carbon atom and an adjacent atom in the ring becomes firmer, the major portions of their affinities being called into play in effecting the ortho linkage. The ortho carbon atoms, therefore, have less residual affinity than is possessed by those in the meta positions. Part of the excess of free affinity possessed by each *meta* carbon atom is used in strengthening the *meta-para* union. The residual valence of the para carbon is thus decreased and its activity is reduced. The surplus free affinity resides upon either the meta, or the ortho and

* Brown and Gibson, *Trans. Chem. Soc.*, **61**, 367 (1892).

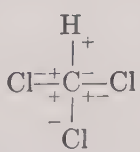
† Flürscheim, *J. Prakt. Chemie* (2), **71**, 497 (1905).

para carbon atoms, as determined by the type of union that exists between the ring and the substituent already present.

The electron theory. Ultimately the electron theory will afford a complete explanation of the facts upon which the Brown-Gibson rule is based. At the present time a thoroughly satisfactory explanation cannot be made, for we have insufficient evidence concerning the distribution of the thirty valence electrons in the benzene molecule.

Systematic attempts to determine the electronic structures of atoms and molecules have been made by L. W. Jones, H. S. Fry, Julius Stieglitz, J. Stark, G. N. Lewis, Falk and Nelson, and others. But up to the present time no agreement has been reached. The fundamental question concerning the nature of the chemical bond is still unanswered. Important papers dealing with various phases of the subject are listed below.*

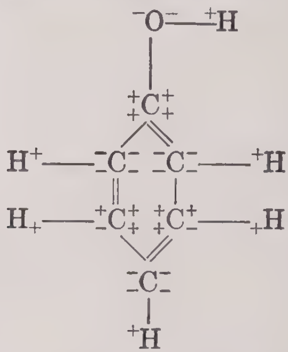
Stieglitz regards chemical union as due to the complete passage of an electron from one atom to another rather than the sharing of electrons between the atoms involved. In harmony with this view each atom in a compound may be represented as having an integral number of unit positive charges corresponding to the number of electrons it has lost or an integral number of negative charges corresponding to the number of electrons gained. Thus the formula of chloroform, $CHCl_3$, might be written:



The signs indicate that the carbon atom has acquired an electron

* W. A. Noyes, *J. Am. Chem. Soc.*, **39**, 880 (1917); *ibid.*, **42**, 991 (1920); L. W. Jones, *Am. Chem. J.*, **48**, 26 (1912); *ibid.*, **50**, 440 (1913); *J. Am. Chem. Soc.*, **36**, 1258 (1914); H. S. Fry, *Zeit. physik. Chem.*, **76**, 385 (1911); *J. Am. Chem. Soc.*, **34**, 669 (1911); *ibid.*, **36**, 257 (1914); *ibid.*, **37**, 883 (1915); Falk and Nelson, *J. Am. Chem. Soc.*, **32**, 1637 (1910); *ibid.*, **33**, 1150 (1911); *ibid.*, **36**, 209 (1916); *ibid.*, **37**, 1732 (1915); Nelson Beans and Falk, *J. Am. Chem. Soc.*, **35**, 1810 (1913); M. L. Huggins, *J. Am. Chem. Soc.*, **45**, 264 (1923); J. J. Thomson, *Phil. Mag.*, **27**, 757 (1914); G. N. Lewis, *J. Am. Chem. Soc.*, **35**, 1448 (1913); *ibid.*, **38**, 762 (1916); Bray and Branch, *J. Am. Chem. Soc.*, **35**, 1440 (1913); J. Stark, *Die Elektrizitat in chemischen Atom.*, Leipzig (1915); Arthur Michael, *J. Am. Chem. Soc.*, **42**, 1223 (1920); I. Langmuir, *J. Am. Chem. Soc.*, **41**, 868 (1919); *ibid.*, **42**, 274 (1920); Jones and Sneed, *J. Am. Chem. Soc.*, **39**, 674 (1917); Bohr, *Phil. Mag.*, **26**, 1, 476, 857 (1913); Parsons, *Smithsonian Collection*, **65**, No. 11 (1915); E. D. Eastman, *J. Am. Chem. Soc.*, **44**, 445 (1922); J. J. Thomson, *Phil. Mag.*, **46**, 497 (1923).

from hydrogen and yielded an electron to each of the three chlorine atoms. The formula for phenol

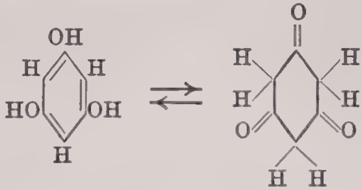


indicates the transference of an electron from hydrogen to oxygen and from carbon atom (1) to the oxygen atom of the hydroxyl group. The hydrogen is positive and the oxygen negative in this molecule. For reference, let us number the carbon atoms consecutively from one to six, beginning with the atom to which the hydroxyl group is attached and passing in a clockwise direction around the ring. Carbon atom (1) has yielded an electron not only to the oxygen atom but it has given one electron to carbon (6) and two to carbon (2). Carbon (2) has gained one electron from the hydrogen attached to it, one more from carbon (3), and two from carbon (1). Carbon (1) is therefore completely positive (fully oxidized), whereas carbon (2) is entirely negative (that is, in its lowest state of oxidation). Carbon (3) is in an intermediate state represented by three positive charges and one negative. With this introduction to the use of plus and minus signs in indicating the displacements of electrons the student will be able to understand the argument as presented in the following paragraphs from Stieglitz's paper.*

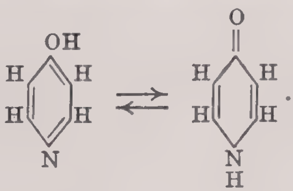
There is, however, an electrical basis for the Brown-Gibson rule of substitution which may be developed by the application to benzene derivatives of facts determined experimentally in the simple field of the aliphatic series of organic compounds and without a single *ad hoc* or specifically new assumption. The development of this interpretation may well start with a consideration of the behavior of phenols. Phenols are in every respect the aromatic analogues of aceto-acetic ester. They form the same type of deeply

* Stieglitz, *J. Am. Chem. Soc.*, **44**, 1299 (1922).

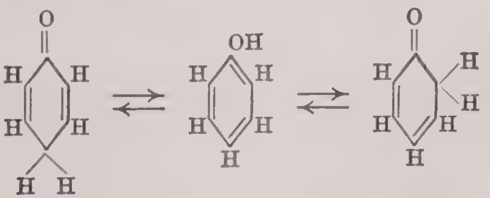
colored ferric salts; they form enol-keto tautomers, as is most clearly illustrated by the behavior of phloroglucinol



about whose structure as a triphenol or triketone the usual controversy is to be found in the literature, resulting from the tautomeric behavior of the compound. . . . A minor point of difference between phenol and acetoacetic ester is that it no doubt forms para as well as ortho tautomeric ketones, exactly as oxypyridine is known to form the pyridone tautomer,



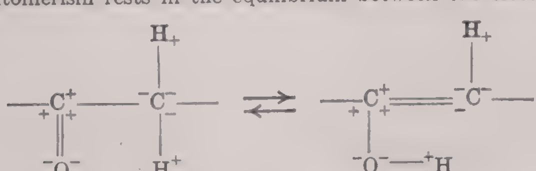
We have then for phenol the system



III I II

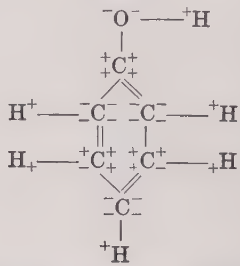
in which structure I presumably is by far the most stable.

Now, the formation of ketonic tautomers by phenol, resorcinol, phloroglucinol, etc., means that the C=O group has the electronic structure $\mathrm{C}\ddagger\!=\!\mathrm{O}$ as in all ketones, and that consequently *the end of one of the double* bonds of Formula I attached to the C—OH carbon atom is *positive.* The very fact of tautomerism rests in the equilibrium between the electrical forces



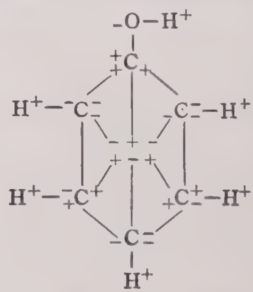
Further, there is a well-known noteworthy tendency of all atoms to become either wholly negative or wholly positive, intermediate forms being relatively unstable and tending to revert to the extremes. . . . We can

conclude, therefore, that both in aceto-acetic ester and in phenol both of the bonds in the double bond of the enol are positive at the C—OH ends. Since in phenol the double bond oscillates (Kekulé, and confirmed by Fry), we have all four valences of the C—OH carbon atom as positive valences. The symmetry of the benzene nucleus having been amply demonstrated experimentally, we thus have for phenol



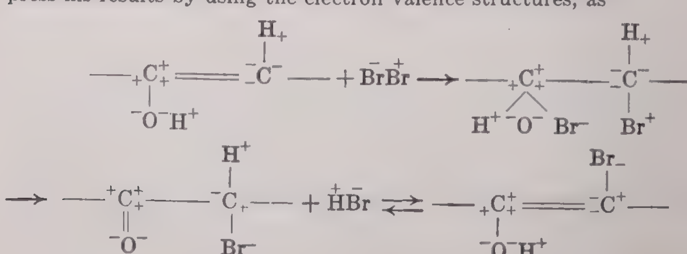
(IV)

It is to be distinctly understood that we have oscillations of the double bonds from side to side and that consequently the centric structure represents an intermediate position of the unsaturated valences.

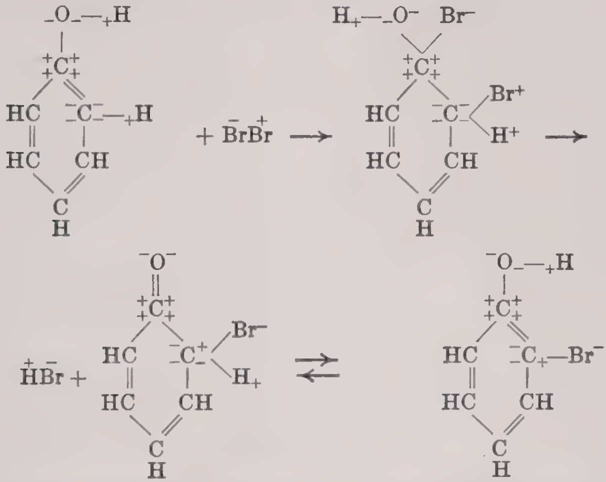


For all we know, this may represent the structure of by far the largest proportion of the molecules of a benzene derivative — but the *chemically active* molecules have the structure IV. . . .

Kurt Meyer in an excellent extended investigation has proved that bromination of aceto-acetic ester proceeds quantitatively by absorption of bromine by the enol double bond, followed by the loss of hydrobromic acid to form a ketone (not directly a brominated enol). We may now express his results by using the electron valence structures, as



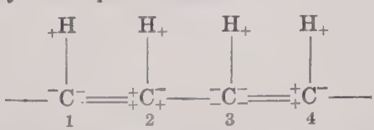
We may apply this proved course of the reaction for aceto-acetic ester without change to the bromination of phenol.



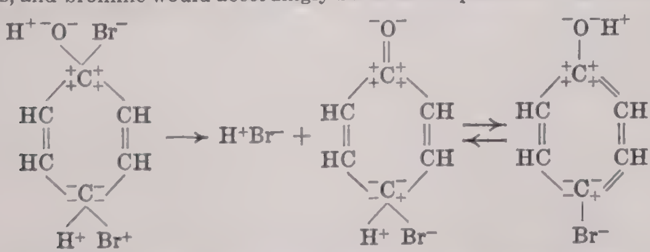
The second ortho position is brominated in exactly the same way.

For the para reactivity, we have to apply the facts discovered by Bayer and Thiele, which have been summarized in Thiele's theory of "conjugated double bonds" but which need no specific assumptions as to a special kind of double bond to understand their behavior. . . .

The fact is simply that a pair of double bonds as in



is known to absorb hydrogen, halogen etc., at atoms 1 and 4 and not at 1 and 2, or 3 and 4. Now in phenol (IV) we have such conjugated double bonds, and bromine would accordingly be added in positions 1 and 4 to form



Again, by loss of hydrogen bromide a ketone (*para*) is first formed, which reverts to the normal tautomeric enol, *para*-bromphenol.

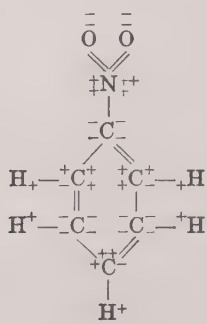
Similarly, in the nitration of phenol, we have absorption of HO and NO_2 at positions 1 and 2 or 1 and 4, respectively, *ortho*- and *para*-nitrophenol

resulting. Nitric acid acts here characteristically through its basic ionization, a view which is well confirmed by the use of concentrated nitric acid, fuming nitric acid, and concentrated sulphuric acid with nitric acid as the best nitrating reagents. . . .

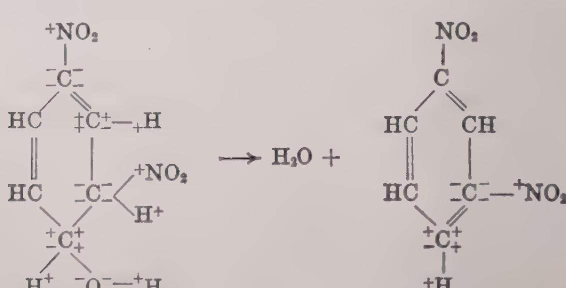
The Crum Brown-Gibson rule of substitution for phenols, favoring, ortho-ortho-para substitution, rests therefore on the electric structure, IV, of phenol, which is here recognized as the favored one because the negative substituting group, –O–, develops two positive charges on the carbon atom holding it, and these in turn favor complete positive character of the carbon atom in question, in conformity with the universal tendency of a charged atom to be positive or negative, in consequence of the structural relations of the atoms.

The other benzene derivatives, C_6H_5X, in which *ortho-ortho-para* substitution is favored, all have a negative X, as $\bar{N}H_2$, $\bar{C}l$, $\bar{B}r$, etc., which has, of course, the same effect as $\bar{O}H$.

As to the second group of benzene derivatives, C_6H_5Y, in which the formation of meta-meta derivatives occurs, we can obtain a similar electron valence basis for the rule by a study of nitrobenzene and its derivatives. From nitric acid $H_{+}{-}O{-}{}_{+}N^{\ddagger}_{\ddagger}(O^{=}_{-})_2$ we obtain the positive nitro group ${}_{+}N^{\ddagger}_{\ddagger}(O^{=})_2$. . . . We have then as the stable form of nitrobenzene and similar derivatives



We can easily see that, in further nitration, meta-dinitrobenzene would be the favored isomer formed.



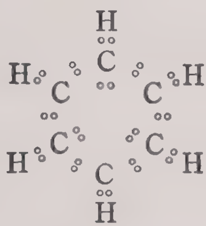
In the same way 1, 3, 5-trinitro-benzene would be formed. In the other benzene derivatives, C_6H_5Y, favoring meta substitution, Y is similarly a positive radical, as found for $_{+}NO_2$.

Latimer and Bray have presented a somewhat different point of view, based upon the following considerations:

1. There are thirty valence electrons in the benzene molecule — an average of five electrons per carbon atom.

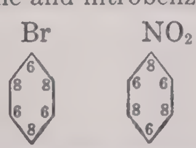
2. In stable molecules atomic nuclei are not associated with odd numbers of electrons. There is a tendency for each carbon atom to complete its octet, but when this is impossible, there will be a distribution of such a character as to leave an even number of electrons for each atom.

3. The benzene molecule is symmetrical. In harmony with these facts the distribution of the electrons is assumed to be as follows:



Each alternate carbon atom has a complete octet; each of the others has a sextet. The lone pairs of electrons may shift from one carbon atom to the next, the result being analogous to the effects of shifting the alternate double bonds in the Kekulé formula. When an atom, like bromine, which holds a complete octet of electrons, is substituted for hydrogen, the carbon to which it is attached retains only six electrons; the *para* and the two *ortho* carbon atoms each having eight. When the atom substituted for hydrogen in the ring does not hold a group of eight electrons, the nuclear carbon to which it is attached will have a complete octet.

Thus for brombenzene and nitrobenzene we have



Direct substitution always results in attachment of the entering group to carbon having a complete octet. When the first

substituent is introduced, the carbon atom involved in the reaction will retain its octet if the atom attached to it is still deficient in electrons. But if, in the new compound, the atom substituted for hydrogen is surrounded by a group of eight electrons, then a shift will occur reducing to six the number of electrons retained by the carbon to which the substituted atom is attached. With the formation of a monosubstitution product the possibility of an electronic rearrangement disappears. In the substituted ring the six and eight positions are relatively fixed. The eight positions are *meta* to a nitro-group and *ortho-para* to bromine, and this orientation of electrons determines the position to be taken by the next entering group.

Latimer and Bray avoid the assumption that benzene is a polar compound, but it is obvious that we might assign a plus charge to each carbon atom possessing six electrons and a negative charge to each carbon having a complete octet. The arguments presented by Stieglitz could then be applied to this formula almost without modification.

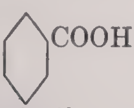
Enhanced activity. Bromine acts slowly upon benzene, forming brombenzene and hydrobromic acid. A catalyst is required to accelerate the reaction in order to make it a practical method of preparation. If we introduce a hydroxyl or an amino group into the ring, then the ortho and para hydrogen atoms of the resulting phenol or amine are at the same time rendered more reactive. Even a dilute solution of bromine in water immediately precipitates tribromphenol and tribromaniline from solutions of phenol and aniline.

The chlorine in chlorbenzene is very firmly held; but chlorine in trinitro-chlorbenzene is extremely reactive. A commercial method for making picric acid is based upon this increased activity of the halogen atom. Chlorbenzene is nitrated and the halogen is subsequently replaced by hydroxyl by merely boiling with water. The para hydrogen in an amine or phenol is much more active than hydrogen in unsubstituted benzene. Upon this enhanced activity depends the formation of the azo dyes, triphenylmethane dyes, and phthaleins.

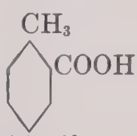
Diminished activity. When carbon tetrachloride is warmed with benzene in the presence of aluminum chloride (Friedel and Crafts), or with brombenzene and sodium (Fittig), three of the chlorine atoms are replaced by phenyl radicals. The fourth chlorine atom is not removed by these reagents. The

ease with which triphenyl chlormethane, ϕ_3CCl, triphenylmethane, ϕ_3CH, and triphenyl carbinol, ϕ_3COH, are formed and the failure to secure tetraphenylmethane, ϕ_4C, under similar conditions, led Victor Meyer to the conclusion that there was not room enough for the direct attachment of four phenyl radicals to a single carbon atom. He believed that three such groups and one smaller radical could be packed into the space around the methane carbon, without forcing any one of them out to a point beyond the central atom's range of attraction, but the fourth large group was excluded for lack of room. Meyer referred to this phenomenon as steric hindrance.

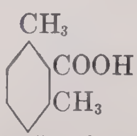
The diminished activity of an atom or group between two side chains on the benzene ring was explained also as due to steric hindrance. Aniline and toluidine form addition products with alkyl halides, but if side chains be introduced in both positions, ortho to the amino group, addition of an alkyl halide either fails to occur or takes place very slowly. Similarly, benzoic acid, with an alcohol, readily forms an ester; *o*-toluic acid reacts more slowly and 2, 6-xylic acid can hardly be esterified at all by the usual direct method.



Benzoic acid



o-toluic acid



2, 6-xylic acid

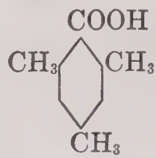
It has been shown, however, that the failure to form such compounds as tetraphenylmethane and esters of di-ortho substituted acids is not due to lack of room for an entering group. By indirect means Gomberg made tetraphenylmethane, and instead of being an unstable compound, as would be expected if the phenyl groups were crowding each other away from the central carbon atom, it proved to be a very stable substance, melting at 282° and distilling unchanged at 431°. A di-ortho substituted acid which fails to form an ester when treated with alcohol may be esterified by the action of its silver salt on ethyl iodide, and, when formed, the ester is not readily hydrolyzed. Steric hindrance, therefore, is not due to insufficient space for the attachment of a large group. It is a retarding of the rate of change due in some degree, perhaps, to obstruction afforded by the surrounding groups, but due primarily to chemical in-

fluences of the ortho substituents, comparable to the accelerating effects of the various groups discussed under "enhanced activity."

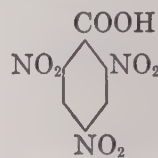
The interference or hindrance varies with the chemical nature of the groups occupying the ortho positions, and in its effect upon the rate of ester formation from aromatic acids it increases in the following order: chlorine, alkyl radicals, hydroxyl, bromine, iodine, nitro group.

Benzoic, mesitylenic, and trinitrobenzoic acids were warmed with methyl alcohol and hydrogen chloride for three hours. The per cent of acid esterified is indicated under each formula:

Benzoic 90%

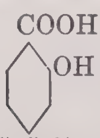


Mesitylenic 48%

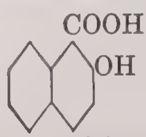


Trinitrobenzoic 6%

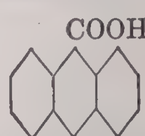
Results of another esterification experiment are given below. The acids were mixed with methyl alcohol and hydrogen chloride, and held at a temperature of 20° for eight hours:



Salicylic 34%

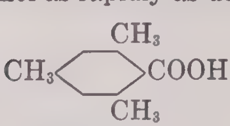


β-Hydroxynaphthoic 3%

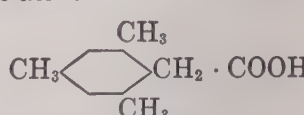


α-Anthracene carboxylic 0%

Ortho substituents do not retard esterification if the carboxyl group is remote from the ring. It is difficult to esterify mesitylenic or mesityl-formic acid, but mesityl-acetic acid reacts with alcohol as rapidly as does benzoic acid:



Mesityl-formic
(slowly esterified)



Mesityl-acetic
(rapidly esterified)

This effect may be accounted for on the purely physical basis of steric hindrance — the carboxyl in mesityl-acetic acid being beyond the range of obstruction due to the methyl radicals. On the other hand, removal of the carboxyl group from the ring would virtually nullify, or it might even reverse,

the chemical influence that the ortho substituents exert upon it. If steric hindrance were due to physical rather than to chemical influences, then long side chains should be much more effective than short ones. As a matter of fact, there is little, if any, difference in the potency of aliphatic hydrocarbon radicals, and no alkyl radical however long produces a hindering influence comparable to that of the nitro group.* On the other hand, Hufferd and Noyes† have measured the rates of esterification of xylic acids and have obtained results in strict accord with predictions that would be made on the basis of Meyer's theory that ortho substituents actually shield the carboxyl group from reagents that would otherwise reach it.

* For a summary of the literature relating to steric hindrance, see A. W. Stewart, Stereo-Chemistry.

† Hufferd and Noyes, *J. Am. Chem. Soc.*, **43**, 925 (1921).

FREE RADICALS

In 1848 Frankland made an effort to isolate the ethyl radical, C_2H_5, by removing bromine from ethyl bromide through the agency of zinc. Zinc bromide was formed, but instead of securing free ethyl radicals he obtained either butane, $C_2H_5 \cdot C_2H_5$, or zinc ethyl, $Zn(C_2H_5)_2$. For a period of fifty years after an account of this unsuccessful attempt was published, chemists continued the search for compounds of trivalent carbon. Negative results gradually established the doctrine that a free carbon radical was incapable of independent existence.

In 1900, Gomberg * prepared hexaphenylethane by the action of finely divided metallic zinc or silver on a solution of triphenylchlormethane:

$$2(C_6H_5)_3CCl + 2Ag \longrightarrow (C_6H_5)_3C \cdot C(C_6H_5)_3 + 2AgCl.$$

Unlike an ordinary saturated hydrocarbon, this compound dissolved in benzene or ether with the development of color (yellow). The color was discharged when the solution was exposed to the air and a crystalline peroxide,

$$(C_6H_5)_3C \cdot O \cdot O \cdot C(C_6H_5)_3,$$

precipitated. The compound absorbed bromine and iodine, with the formation of triphenylmethylhalides, $(C_6H_5)_3CBr$ and $(C_6H_5)_3CI$. It, therefore, behaved like a highly unsaturated compound, but, unlike compounds having multiple bonds, it formed halogen addition products with only one halogen atom in each molecule. This unusual behavior of the hydrocarbon led Gomberg to conclude that the solution contained free half molecules of hexaphenylethane, namely, triphenylmethyl, $(C_6H_5)_3C—$. Further study confirmed the opinion that in non-polar as well as in ionizing solvents hexaphenylethane dissociates, establishing an equilibrium between the free radicals and the undissociated molecules.

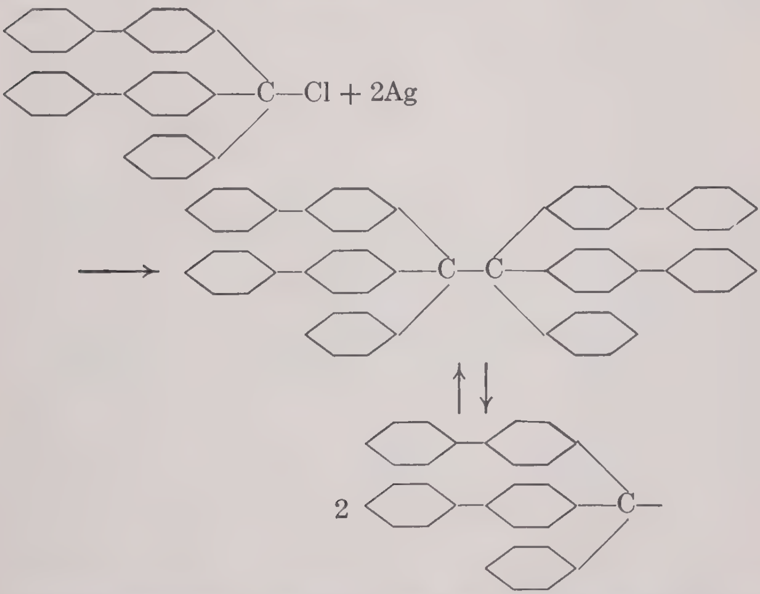
$$(C_6H_5)_3C—C(C_6H_5)_3 \rightleftarrows 2(C_6H_5)_3C—$$

The molecular weight determined by the cryoscopic method was found to be 480 in benzene and 407 in naphthalene. The

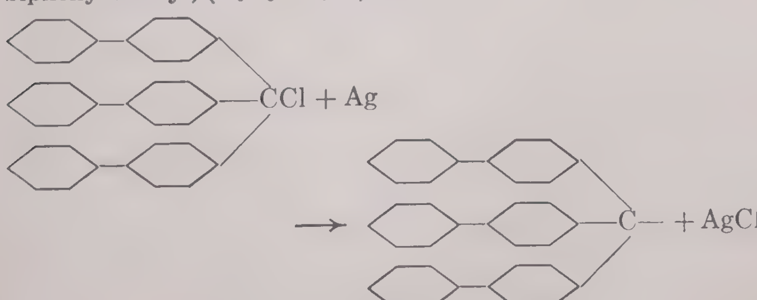
* Gomberg, *Jour. Am. Chem. Soc.*, **22**, 757 (1900). *Ber.*, **33**, 3150 (1900); *ibid.*, **35**, 1839, 3914, 757 (1900).

calculated value for the undissociated molecule is 486. The small volume of oxygen required to discharge the color also indicated slight dissociation.

With more complex groups attached to the tertiary carbon, much larger yields of free radicals were obtained. Thus, for example, phenyldibiphenylchlormethane, when dissolved in benzene and treated with molecular silver, yields a product which is 80 per cent dissociated.



Tribiphenylmethyl chloride with silver in dry benzene yields the free radical only. That is to say, hexabiphenylethane in dilute benzene solution is 100 per cent dissociated into tribiphenylmethyl, $(C_6H_5 \cdot C_6H_4)_3C$—.

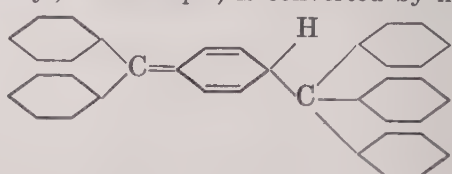


The quantity of oxygen absorbed by the solution is the most reliable measure of the dissociation. In liquid sulphur dioxide and in other ionizing solvents these compounds are all good conductors of electricity, the dissociation being of such character that the pair of electrons constituting the valence bond between the ethane carbon atoms are both held by the same radical (the negative ion). In non-polar solvents the dissociation results in the formation of two identical electrically neutral radicals.

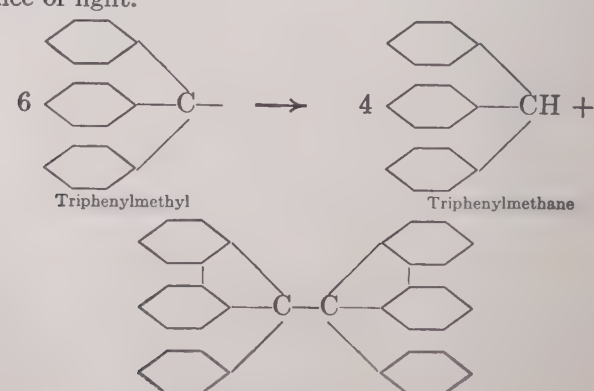
$$(C_6H_5)_3C{:}C(C_6H_5)_3 \nearrow (C_6H_5)_3C^+ \;+\; (C_6H_5)_3C{:}^- \quad \text{in } SO_2$$

$$(C_6H_5)_3C{:}C(C_6H_5)_3 \searrow (C_6H_5)_3C^{\cdot} \;+\; (C_6H_5)_3C^{\cdot} \quad \text{in benzene}$$

The preparation of free radicals involves a fine technique. They combine rapidly not only with air, water, and halogens, but form complex addition products with many types of so-called saturated organic compounds such as phenols, alcohols, esters, and some ethers. They are sensitive to light and heat, undergoing various types of rearrangement or decomposition. Triphenylmethyl, for example, is converted by hydrogen ions into

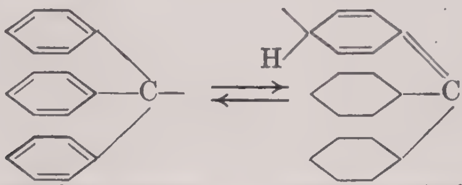


It decomposes into two saturated hydrocarbons under the influence of light.



Dibiphenylene-diphenylethane

All of these free radicals yield colored solutions. One or two representatives of the group are colorless at low temperatures, but color develops when they are warmed. Gomberg attributes the color in every instance to the formation of the quinoid structure in one of the rings, assuming an equilibrium of the following type:



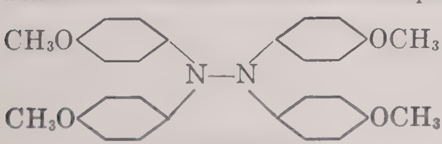
Benzoid form (colorless) Quinoid form (colored)

Lewis attributes the color to absorption of light energy by the odd or unpaired valence electrons.*

Wieland† prepared tetraphenylhydrazine,

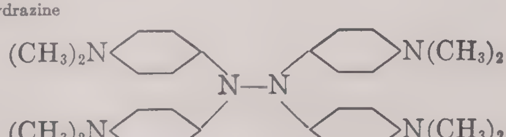
$$(C_6H_5)_2N:N(C_6H_5)_2,$$

to determine whether this compound would dissociate into radicals containing divalent nitrogen. Molecular weight measurements gave no evidence of such dissociation. The compound reacts with triphenylmethyl, however, forming triphenylmethyldiphenylamine, $(C_6H_5)_3C \cdot N(C_6H_5)_2$. More convincing evidence of the existence of divalent nitrogen was found in the behavior of some substituted tetraphenylhydrazines, such as:



and

p-Tetraanisylhydrazine



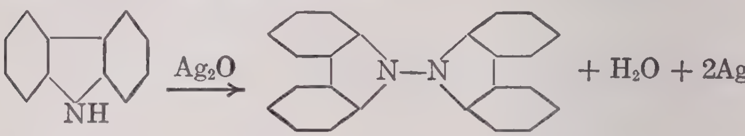
Tetradimethylaminophenylhydrazine

These compounds form addition products and in solution have molecular weights below the calculated values for undissociated molecules.

* Gomberg and Jickling, *J. Am. Chem. Soc.*, **37**, 2575 (1915). Gomberg and Sullivan, *J. Am. Chem. Soc.*, **44**, 1810 (1922). Lewis, *J. Am. Chem. Soc.*, **38**, 783 (1916).

† Wieland and Gambarjan, *Ber.*, **39**, 1499 (1906). Hantzsch, *ibid.*, p. 2478.

Branch and Smith* oxidized carbazole by means of moist silver oxide to secure dicarbazyl.



It was reasonable to assume that this hydrazine derivative might dissociate to a greater extent than did Wieland's compounds. The reaction did not proceed in exact accordance with the above equation. An unsaturated nitrogen compound was formed, but its structure was not definitely established.

A substituted ammonium radical was obtained in the form of an amalgam by McCoy and West.† Tetramethylammonium chloride was decomposed by electrolysis in the presence of a mercury cathode. The radical $(CH_3)_4N$, acting like a free metal, formed an amalgam with the mercury.

Attempts have been made to obtain compounds of univalent oxygen,‡ bivalent arsenic,§ trivalent silicon,** and radicals of other elements, but most of these attempts have been unsuccessful.

Hexaphenylsilicoethane, $(C_6H_5)_3Si \cdot Si(C_6H_5)_3$, displays none of the properties of hexaphenylethane. It is a very stable compound that melts above 300°, has no color in any solvent, and forms no peroxide.

A solution of *bis*-leadtriphenyl, $(C_6H_5)_3Pb \cdot Pb(C_6H_5)_3$, acquires a weak color at high temperatures but forms no peroxide and gives no other evidence of dissociation. The compound is made by heating lead tetraphenyl.

$$2Pb(C_6H_5)_4 \longrightarrow (C_6H_5)_3Pb\text{—}Pb(C_6H_5)_3 + C_6H_5 - C_6H_5$$

* Branch and Smith, *J. Am. Chem. Soc.*, **42**, 2405 (1920).

† H. N. McCoy and F. L. West, *J. Phys. Chem.*, **16**, 261 (1912).

‡ Pummerer and Frankfurter, *Ber.* **49**, 1472 (1914). Porter and Thurber, *J. Am. Chem. Soc.*, **43**, 1194 (1921).

§ Porter and Borgstrom, *J. Am. Chem. Soc.*, **41**, 2048 (1919).

** Schlenk, Renning, and Racky, *Ber.*, **44**, 1179 (1909).

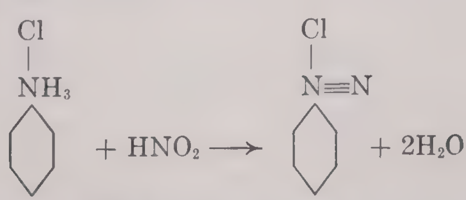
DYES

A dye is a colored compound which is capable either directly, or with the aid of a mordant, of imparting a permanent color to textile fibers. The practical dyer lists such substances in two principal groups: (1) those that dye fibers directly (substantive dyes), and (2) those that require mordants (adjective dyes).

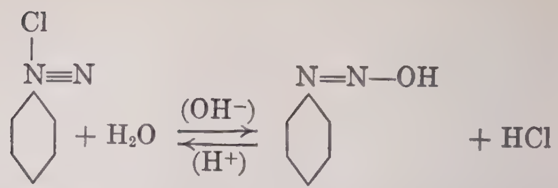
The mordants commonly employed are aluminum, iron, chromium and tin salts, tannic acid, calcium phosphate, albumen, and finely divided silica. The choice of mordant is determined by the character of the dye. There have been many vigorous debates concerning the nature of the union between dyes and textile fibers. The facts seem to indicate that most substantive dyes enter into chemical combination with wool and silk, and many adjective dyes form compounds with mordants. On the other hand, there is evidence that in many cases dyeing is accomplished through physical adsorption of the dye without compound formation.

Azo Dyes

Any primary aromatic amine may be diazotized by nitrous acid (see p. 265). The reaction is usually carried out by adding sodium nitrite to an acid solution of an amine salt. A diazonium salt is thus formed.

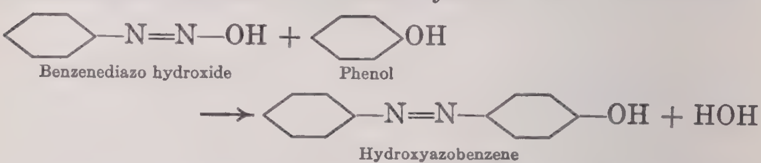


When the excess of acid in the solution is neutralized by the addition of a base, the diazonium salt is converted into a diazo compound. The reaction is reversible. Strong acids regenerate diazonium salts from the diazo compounds.



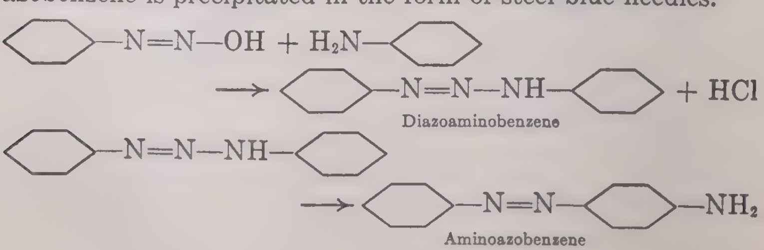
The diazo compound is stable in the presence of weak acids as well as in the presence of bases. Thus, a hydrochloric acid solution of benzenediazonium chloride is converted into benzenediazo hydroxide by the addition of sodium acetate.

The diazo compounds combine with phenols, or naphthols or with aromatic amines to form azo dyes.



It is the hydrogen atom para to the hydroxyl group in the phenol that is replaced. If the para position is occupied by any element or group other than hydrogen, coupling occurs in an ortho position; and if the para and both ortho positions are so occupied, then coupling usually fails to occur and no dye is formed. In rare instances a para substituent is replaced by the diazo group. The same rules apply to the union of a diazo compound with a tertiary amine such as dimethylaniline.

When a primary or secondary amine is coupled with a diazo compound, an intermediate product, known as a diazoamino compound, is usually formed by replacement of hydrogen attached to nitrogen. Thus diazotized aniline combines with unchanged aniline, yielding diazoaminobenzene, in the form of golden-yellow plates. When warmed with hydrochloric acid containing a little aniline hydrochloride, a rearrangement occurs and aminoazobenzene is precipitated in the form of steel-blue needles.



In any case where a diazoamino compound is formed, this rearrangement may be induced by warming a solution of the compound with an excess of the corresponding amine hydrochloride. It is an application of the Hofmann reaction (p. 256).

If we assume that the first reaction between an amine and a diazo compound is a direct addition and that this is followed by a rearrangement, it is not necessary to treat tertiary amines as a special class. Thus with the primary amine ϕNH_2 and the diazo compound ϕ—N=N—OH we obtain the addition product

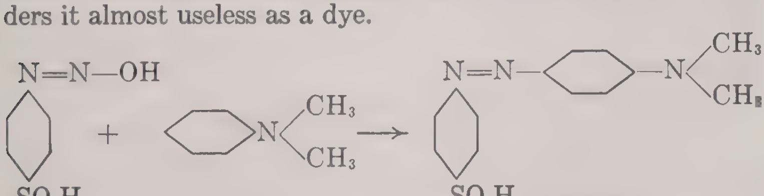
$$\phi\text{—}\overset{\displaystyle OH\ \ H}{\underset{\displaystyle \quad\diagdown N{=}N\text{—}\phi}{N\text{—}H}}$$

. Water is eliminated from this, as from ammonium hydroxide, yielding the diazoamino compound, ϕ—NH—N=N—ϕ, which must be warmed with an acid or an amine salt to induce the rearrangement to an amino-azo compound. With a secondary amine the same reactions occur. In the case of a tertiary amine, ϕNR_2, the addition is assumed to occur giving

$$\phi\text{—}\overset{\displaystyle OH\ \ R}{\underset{\displaystyle \quad\diagdown N{=}N\text{—}\phi}{N\text{—}R}}$$

, but in this case water cannot be eliminated to form a stable diazoamino compound, and as a result the rearrangement occurs at once, yielding the dye.

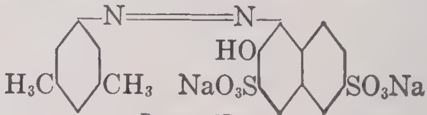
Helianthin. p Dimethylaminoazobenzenesulphonic acid, or helianthin, is prepared by mixing aqueous solutions containing equivalent quantities of diazotized sulphanilic acid and dimethylaniline hydrochloride. The sodium salt of the compound is the yellow dye known as methyl orange. It is used as an indicator in the titration of acids and bases. Its sensitiveness to changes in the concentrations of hydrogen and hydroxide ions — the property that makes it a valuable indicator — renders it almost useless as a dye.



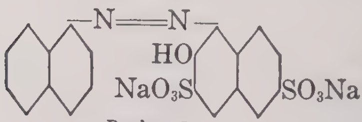
Helianthin

In coupling with α-naphthol and α-naphthylamine, the diazo group enters in position 4 (para to the hydroxyl or amino group). If this position is occupied by any group or element other than hydrogen, or if position 3 or 5 is occupied by

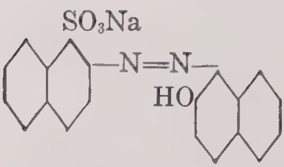
sulphonic acid groups, the union occurs in position 2 (ortho to the hydroxyl or amino group). With β-naphthol or β-naphthylamine, combination takes place in position 1. If this place is occupied, no coupling occurs. The following compounds are typical examples of commercial azo dyes.



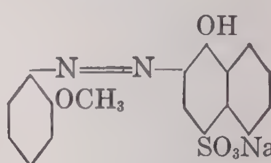
Ponceau 2R



Bordeau 5



Lithol red

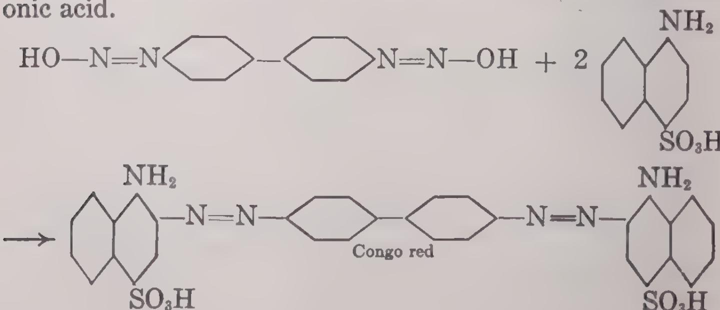


Azocochenille

The intermediates required for the production of these dyes may be determined by inspection of the formulas. Ponceau 2R, for example, is made by coupling diazotized meta-xylidine with the sodium salt of 2, 3, 6-naphtholdisulphonic acid.

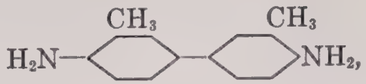
Tetrazo compounds, formed from benzidine, with the naphthols, naphthylamines, and related bodies constitute the Congo group. The latter possess the valuable property of dyeing cotton without mordants.

Congo red is formed from diazotized benzidine and naphthionic acid.

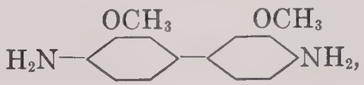


Congo red

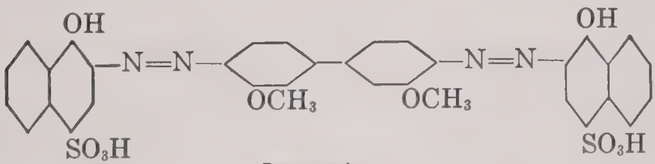
The substitution of tolidine,



or dianisidine,

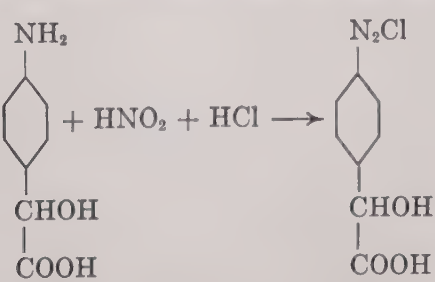


for benzidine shifts the color of the dye toward the violet end of the spectrum. Red predominates in all dyes derived from benzidine by coupling with naphthylamines. The corresponding naphthol derivatives display bluer shades. Tetrazotized dianisidine combines with naphthol sulphonic acid to produce a pure blue.

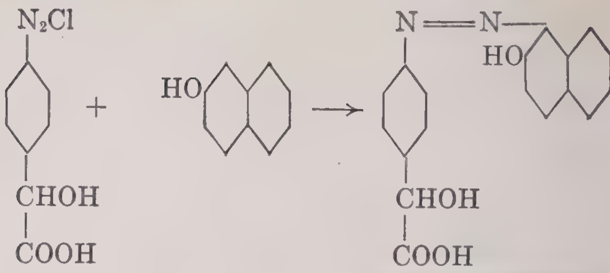


Benzoazurine

A few asymmetric azo dyes have been prepared and methods have been devised for obtaining them in optically active forms.* Amino mandelic acid, $H_2N—C_6H_4—CHOH—COOH$, may be resolved into optically active components by fractional crystallization of its cinchonine salts, and if the pure dextro and lævo forms are separately diazotized and coupled with β-naphthol, brilliant red optically active dyes are produced.



* Porter and Hirst, *J. Am. Chem. Soc.*, **41**, 1264 (1919). Ingersoll and Adams, *J. Am. Chem. Soc.*, **44**, 2930 (1922). Porter and Ihrig, *J. Am. Chem. Soc.*, **45**, 1990 (1923).



β-naphthol-azo-mandelic acid

TRIPHENYLMETHANE DYES

Triphenylmethane, $(C_6H_5)_3CH$, crystallizes in colorless prisms, melting at 93°, and boiling without decomposition at 359°. It is prepared by the following methods:

1. From benzal chloride and benzene in the presence of aluminum chloride.

$$C_6H_5 \cdot CHCl_2 + 2C_6H_6 \longrightarrow C_6H_5 \cdot CH(C_6H_5)_2 + 2HCl$$

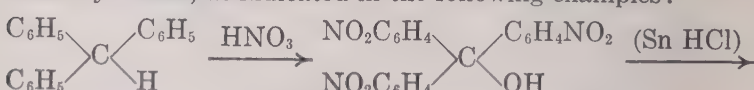
2. From chloroform or bromoform and phenylmagnesium bromide.

$$CHBr_3 + 3C_6H_5MgBr \longrightarrow CH(C_6H_5)_3 + 3MgBr_2$$

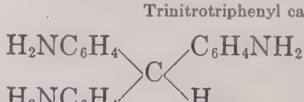
3. From benzaldehyde and benzene in the presence of zinc chloride.

$$C_6H_5CHO + 2C_6H_6 \longrightarrow (C_6H_5)_3CH + H_2O$$

Many beautiful and valuable dyes are derived from this compound. The commercial methods employed in the preparation of these dyes do not involve the synthesis of triphenylmethane, but their relationship to this hydrocarbon has been traced by direct synthesis, as indicated in the following examples:



Triphenylmethane Trinitrotriphenyl carbinol



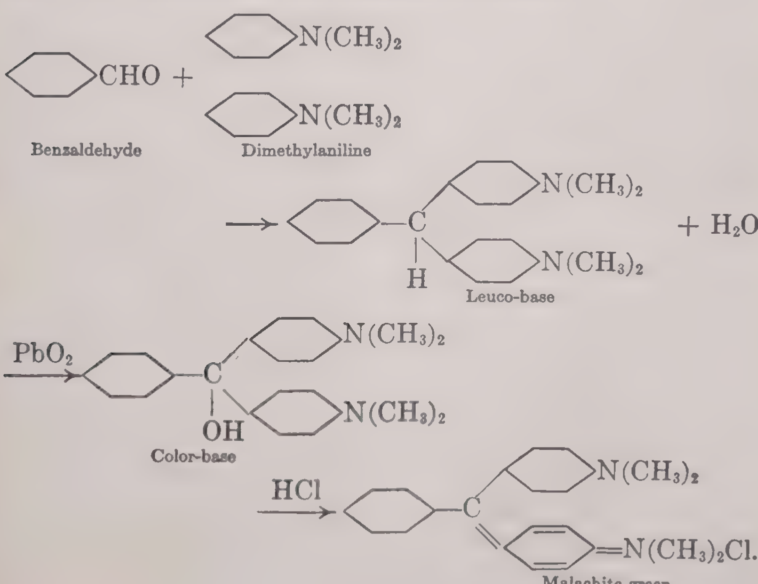
Triaminotriphenylmethane
(leuco-base of p-rosaniline)

Or, beginning with the leuco-base of the dye, the parent substance, triphenylmethane, may be obtained through the diazo reaction.

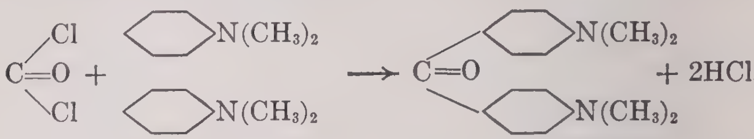
The leuco-base of a triphenylmethane dye is colorless. Mild oxidizing agents, such as nitrobenzene, arsenic acid, and lead peroxide, convert the leuco-base into a carbinol, called a color-base, which is also colorless. Dyes are derived from the color-base by the action of acids. The reaction, which is discussed later, consists of the addition of the acid to an amino group and subsequent elimination of water, with the establishment of a quinoid structure in one of the benzene rings.

The time required to complete the change in structure can be varied between a few seconds and several hours by control of the hydrogen ion concentration and the temperature. The process is reversible. Hydroxide ion reconverts the dye to the colorless color-base, water being taken up by the dye in alkaline solution, and simultaneously the quinoid ring goes back to the benzoid form.

Malachite green. The leuco-base of tetramethyldiaminotriphenylmethane, or malachite green, is formed by the action of zinc chloride on a mixture of benzaldehyde and dimethylaniline. The leuco-base is oxidized to the color-base by lead dioxide and hydrochloric acid. The dye is obtained in the same reaction due to the presence of hydrogen ions which bring about the dehydration and change of structure.

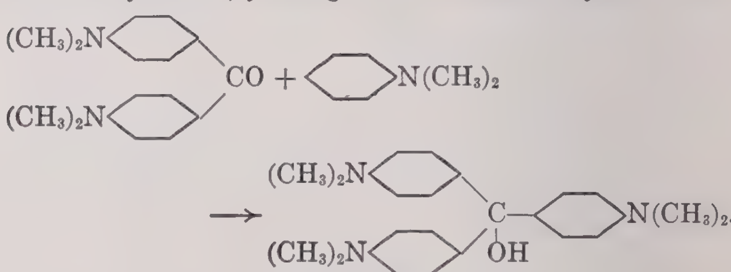


Crystal violet. Phosgene gas is absorbed by dimethylaniline, with the formation of tetramethyldiaminobenzophenone. Hydrogen chloride produced at the same time combines with the excess of dimethylaniline:



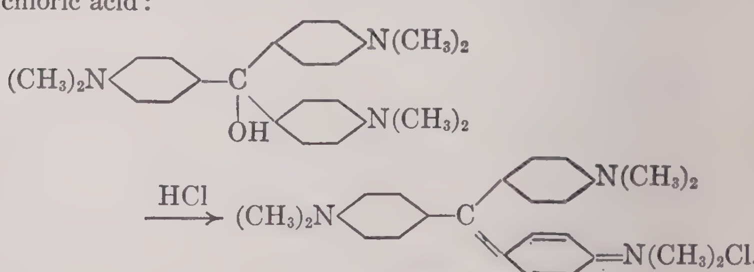
Michler's ketone

In the presence of phosphorus oxychloride, tetramethyldiaminobenzophenone (Michler's ketone) forms an addition product with dimethylaniline, yielding the color-base of crystal violet:



Color-base

The carbinol, or color-base, is converted into the dye, hexamethyltriaminotriphenylmethane, by treatment with hydrochloric acid:



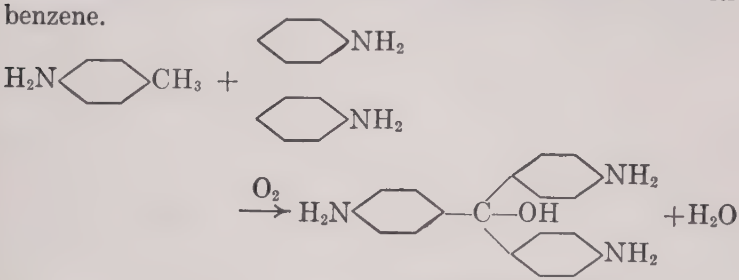
Crystal violet

Like malachite green, and other members of this class, crystal violet dyes silk and wool directly, but cotton is dyed only with the aid of a mordant such as tannic acid.

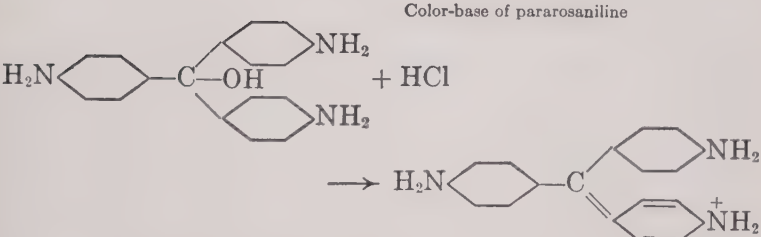
Methyl violet differs from crystal violet only in having one methyl group less in the molecule. It is pentamethyltriaminotriphenylmethane. The crystals have a bronze luster. The

dye is produced from dimethyl aniline by oxidation with cupric chloride, the methane carbon being derived from one of the methyl groups of the amine.*

Pararosaniline. This dye is obtained by oxidizing a mixture of one mol of *p*-toluidine and two mols of aniline with nitrobenzene.

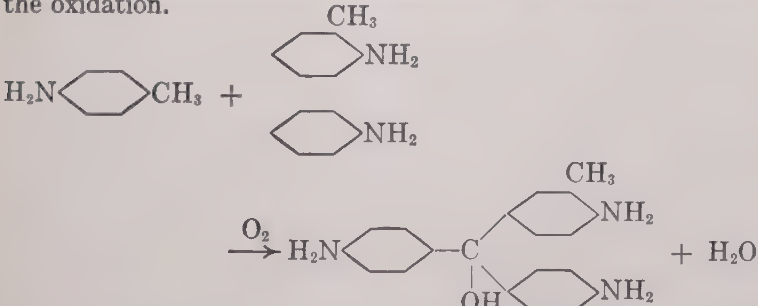


Color-base of pararosaniline



Color-base Pararosaniline

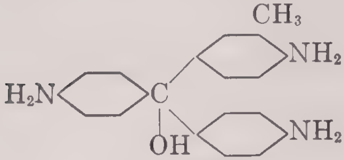
Closely related to this compound is another dye known as rosaniline or magenta. It is produced by oxidizing a mixture containing equi-molecular quantities of aniline, *o*-toluidine, and para-toluidine. As in the case of pararosaniline the methyl group in *p*-toluidine furnishes the methane carbon atom. Mercuric nitrate, nitrobenzene, or arsenic acid may be used to effect the oxidation.



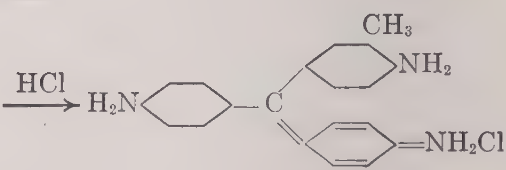
Color-base of magenta

* The mechanism of this reaction is supposed to involve the oxidation of one

The chloride of this color-base forms large crystals, having a bronze, metallic luster.



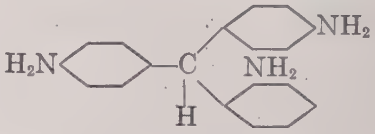
Color-base



Dye (magenta)

Many other dyes of this type have been made by oxidizing various mixtures of aromatic amines. Such mixtures must, however, conform to certain specifications.* In some instances a methyl group attached to nitrogen is eliminated in the process and supplies the methane carbon, but as a rule amines must have a para-methyl group to provide this central atom.

Chrysaniline, a yellow dye, is formed in small quantities as a by-product in the manufacture of pararosaniline. Its production is due to part of the aniline molecules condensing with toluidine through loss of hydrogen ortho to the amino group. The leuco-base of chrysaniline has the formula:

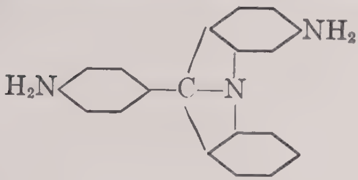


When this compound is oxidized by means of lead dioxide, the hydrogen on the central carbon atom is removed in the formation of water. At the same time, water is formed by removal of hydrogen from the ortho amino group and from an ortho position in one of the other aniline residues. Two rings are

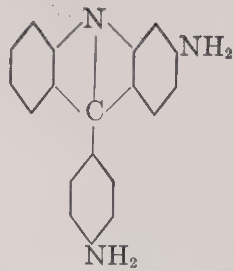
of the methyl groups to formaldehyde, which condenses with the monomethylaniline so formed and with two unaltered molecules of dimethylaniline, forming the dye.

* Cain and Thorpe, Synthetic Dyestuffs, 4th ed., p. 79.

thereby linked together through nitrogen as well as through the methane carbon. The resulting structure is



or



It is a typical representative of the acridine group of dyes.

The colors of the basic triphenylmethane dyes range from yellow to violet, and seem to be determined primarily by the character and number of groups substituted for hydrogen in the amino groups. Yellow, red, green, and violet representatives of the class have been mentioned. A blue dye is obtained by heating pararosaniline with an excess of aniline in acetic acid. The product formed is known as rosaniline-blue and has the following structure:

$$\mathrm{C}\begin{array}{l} \diagup \mathrm{C_6H_4 \cdot NH \cdot C_6H_5} \\ -\mathrm{C_6H_4 \cdot NH \cdot C_6H_5} \\ \diagdown\!\!\diagdown \mathrm{C_6H_4 : NH(C_6H_5)C_2H_3O_2.} \end{array}$$

Only three phenyl groups can be substituted for amino hydrogen, one in each amino group. The corresponding compound, with a phenyl group in only one of the amino groups, is violet and the diphenyl derivative is bluish violet.

Dyes of similar structure, having one or more of the phenyl groups of triphenylmethane replaced by naphthalene and anthracene radicals, have been prepared also. Victoria blue, for example, is made by treating tetramethyldiaminobenzophenone (Michler's ketone) with phenyl-α-naphthylamine; and chrom violet is made in a similar way from tetramethyldiaminobenzhydrol and salicylic acid.

$$\mathrm{C}\begin{array}{l} \diagup \mathrm{C_6H_4 \cdot N(CH_3)_2} \\ -\mathrm{C_6H_4 \cdot N(CH_3)_2} \\ \diagdown\!\!\diagdown \mathrm{C_{10}H_6 : NH(C_6H_5)Cl} \end{array}$$

Victoria blue

$$\mathrm{C}\begin{array}{l} \diagup\!\!\diagup \mathrm{C_6H_4 : N(CH_3)_2Cl} \\ -\mathrm{C_6H_4 \cdot N(CH_3)_2} \\ \diagdown \mathrm{C_6H_3}\begin{array}{l} \diagup \mathrm{OH} \\ \diagdown \mathrm{COOH} \end{array} \end{array}$$

Chrom violet

The amino derivatives of triphenylmethane are basic dyes. The corresponding hydroxy compounds are acidic. They are

less important than the basic dyes; for, as a rule, they fail to impart fast colors to textile fibers. Aurine and rosolic acid, typical members of the group, are obtained from pararosaniline and rosaniline respectively, by the diazo reaction:

$$HC\begin{array}{l} \diagup C_6H_4NH_2 \\ -C_6H_4NH_2 \\ \diagdown C_6H_4NH_2 \end{array} \xrightarrow{HNO_2} \underset{\text{Leuco-base of aurine}}{HC\begin{array}{l} \diagup C_6H_4OH \\ -C_6H_4OH. \\ \diagdown C_6H_4OH \end{array}}$$

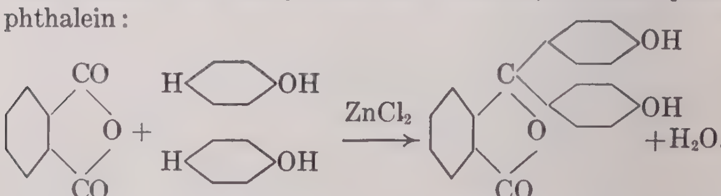
The dye is formed by oxidizing the leuco-base. An intermediate carbinol or color-base is, undoubtedly, produced, but it is unstable and has not been isolated. It loses water at once with the establishment of a quinoid structure:

$$\underset{\text{Color-base}}{HO{-}C\begin{array}{l} \diagup C_6H_4OH \\ -C_6H_4OH \\ \diagdown C_6H_4OH \end{array}} \quad \xrightarrow{-\,H_2O} \quad \underset{\text{Aurine}}{C\begin{array}{l} \diagup C_6H_4OH \\ -C_6H_4OH. \\ = C_6H_4:O. \end{array}}$$

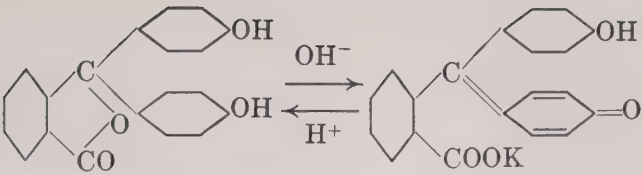
This reaction is reversed and a salt of the carbinol is formed in the presence of acids. The color-bases of the monohydroxy and dihydroxy triphenylmethane derivatives are fairly stable and are known in the free state. The acidic dyes are colored in alkaline and colorless in acid solution.

The Phthaleins

Phenolphthalein. Phenol condenses with phthalic anhydride, when heated with anhydrous zinc chloride, to form phenolphthalein:



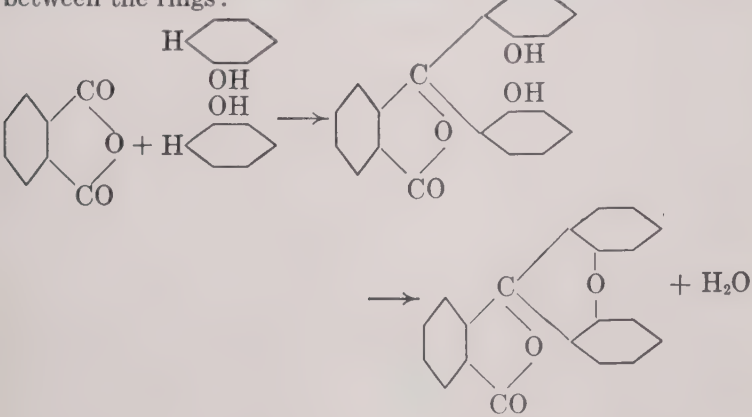
The compound is colorless in neutral and in acid solutions and red in alkaline solutions. It is used extensively as an indicator, for the color change is almost instantaneous and it occurs within a very narrow range of hydrogen and hydroxide ion concentrations, near the true neutral point. A base acts upon phenolphthalein, forming a salt, eliminating a molecule of water, and thereby establishing a quinoid structure. Acids reverse the process:



Colorless Red

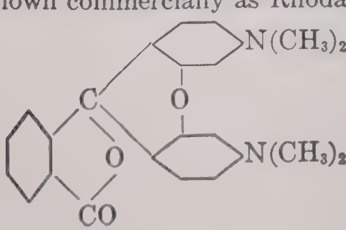
The salt ionizes and is quite soluble, but the acid, assuming the anhydride form, is unionized and only slightly soluble in water. The development of color, however, is not due to the ionization of the salt; it depends upon the production of the quinoid structure. Solid phenolphthalein has a pale yellow color. It melts at 250°.

Fluoran. Condensation of phenol with phthalic anhydride occurs to some extent in the ortho position, and the resulting phthalein loses water spontaneously, forming an oxygen linkage between the rings:

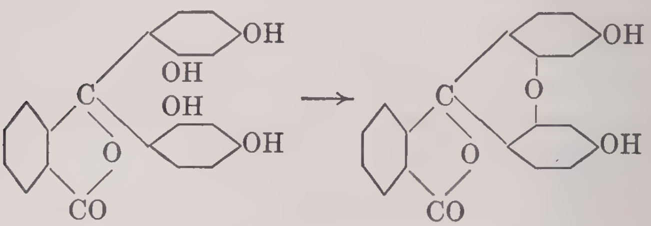


Fluoran

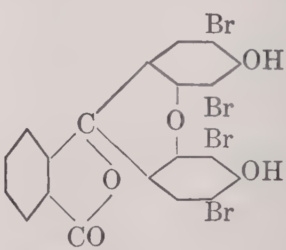
The ortho condensation becomes the main reaction if, instead of using phenol, we employ a meta-aminophenol. Thus, for example, dimethyl-meta-aminophenol and phthalic anhydride yield the dye known commercially as Rhodamine B:



Fluoresceïn. Resorcin couples with phthalic anhydride, the point of attachment being ortho to one and para to the other of the hydroxyl groups. At the same time water is eliminated from the ortho hydroxyl groups and fluoresceïn is produced:



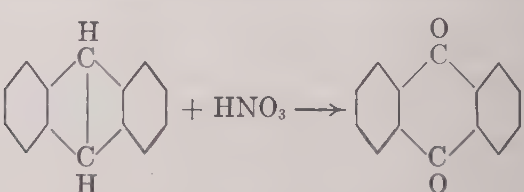
An alkaline solution of the dye appears green by reflected light and red by transmitted light. It is easily brominated, being thereby converted into the beautiful red dye, eosine:



Eosine

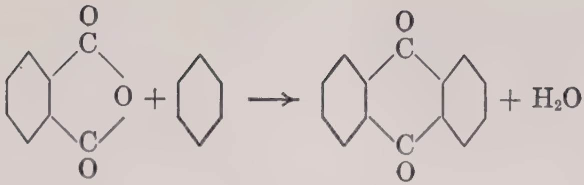
Alizarin Dyes

Nitric acid oxidizes anthracene to anthroquinone (p. 244).

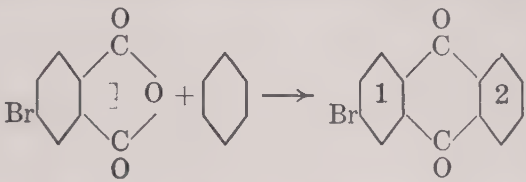


Anthracene Anthraquinone

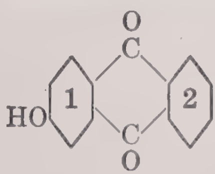
The structure of anthraquinone is established by its synthesis from phthalic anhydride and benzene, in the presence of aluminum chloride, and by a study of the oxidation products of its derivatives.



Brom-orthophthalic anhydride and benzene yield brom-anthraquinone:

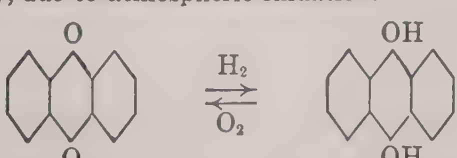


The bromine may be replaced by heating with potassium hydroxide, yielding hydroxyanthraquinone:



From its origin we know that the two CO groups are attached to ortho carbon atoms in nucleus 1. On oxidation by nitric acid, this compound yields phthalic acid and not hydroxy phthalic acid. Nucleus 1, the substituted ring, is the one that is destroyed in the process, and since the oxidation product is ortho phthalic acid, the two CO groups must be attached to ortho carbon atoms in nucleus 2.

Anthraquinone is a yellow, crystalline substance which melts at 285°. When warmed with zinc dust in alkaline solution, it is reduced to anthraquinol, the sodium salt of which has a deep red color. If the red solution is shaken with air, the color fades rapidly, due to atmospheric oxidation.

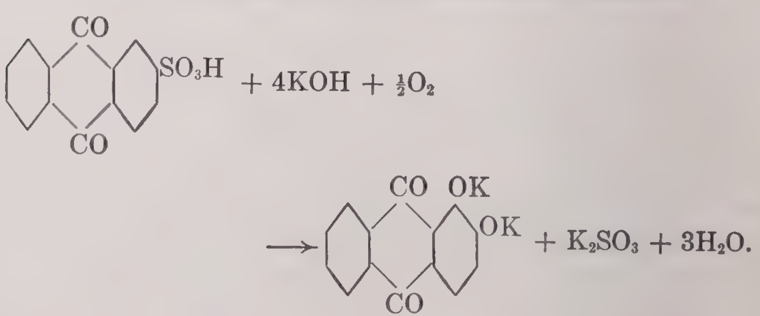


Anthraquinone   Anthroquinol

The most important derivative of anthraquinone is alizarin, a compound that forms, with metallic oxides, beautiful, insoluble dyes. Textiles to be dyed are mordanted with metallic oxides, or with salts that are readily hydrolyzed. The mordanted cloth is then immersed in a solution or suspension of alizarin. The color produced in the fiber depends upon the mordant used. Aluminum and tin oxides yield red colors, calcium oxide, blue, ferric oxide, violet-black, and chromium oxide, a claret color.

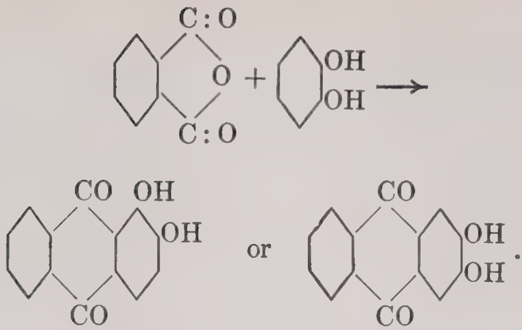
Alizarin was formerly obtained from madder roots, and was the most highly prized vegetable dye known to the ancients. During the first half of the nineteenth century, the annual production of madder was approximately 70,000 tons. In 1869 alizarin was synthesized by Graebe and Liebermann, and independently by Perkin. It is now made in large quantities by modifications of their methods, and, as a result, the cultivation of madder has been abandoned.

Sulphuric acid acts upon anthraquinone to produce β-anthraquinone sulphonic acid,* and this, when fused with potassium hydroxide, in the presence of air, yields a salt of alizarin:



The presence of two hydroxyl groups in alizarin is proved by its analysis, and by its formation from phthalic acid and catechol. The hydroxyl groups must occupy ortho positions, as they do in catechol, but the method of preparation does not settle the question as to whether the two hydroxyl groups are in α-β, or in β-β positions:

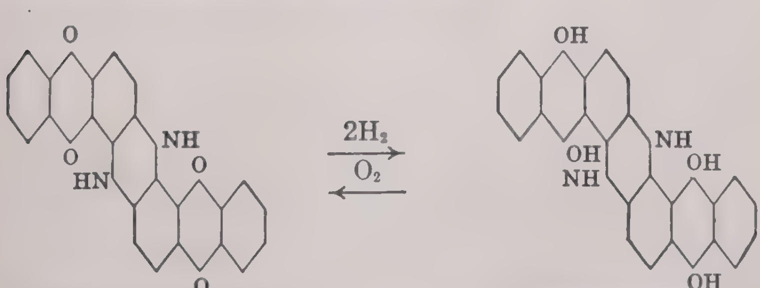
* An α-sulphonic acid is produced when the sulphonation is catalyzed by a mercury salt. The catalyst in this case apparently changes the course of the reaction. As a matter of fact both sulphonic acids are formed. But the two reactions are not equally catalyzed by the mercury salt.



I II

Alizarin forms two mono-nitro derivatives, and in each case the nitro group enters the ring to which the hydroxyl groups are attached; for on oxidation they yield phthalic acid and not nitrophthalic acid. From formula II, only one mono-nitro compound could be made by substitution in the oxidized ring, but two isomeric nitroalizarins would be expected from formula I. Alizarin is, therefore, α-β-dihydroxyanthraquinone, corresponding to formula I. Alizarin can be made by fusing a mixture of anthraquinone, potassium hydroxide, and sodium chlorate. In this method the sulphonation process is avoided.

Indanthrene, a dark blue dye, is formed when β-aminoanthraquinone is fused with potassium hydroxide and sodium nitrate. It is very stable, resisting the action of oxidizing agents, acids, and alkalies, even at temperatures above 300°. It is reduced by sodium hyposulphite in alkaline solution to a hydroxy derivative, which is a valuable vat dye. A vat dye develops its color in the fiber by atmospheric oxidation, after the fabric is removed from the dye bath.

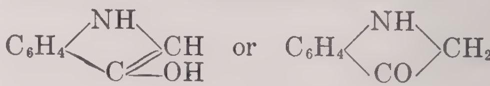


Indanthrene (insoluble blue dye)

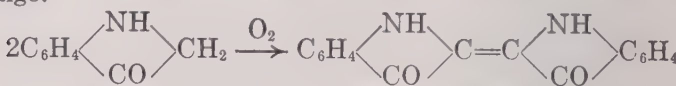
Anthrahydroquinoneazine (soluble yellow vat)

INDIGO

Indigo, obtained from the leaves of indigo plants, has been known for many centuries. Its value depends not only upon its beautiful blue color, but also upon its stability. It is not changed by acids nor alkalies nor is it faded by light. It occurs in the plant as a glucoside, indican, $C_{14}H_{17}O_6N$, which, in the presence of an enzyme occurring with it, is hydrolyzed by warm water to dextrose, $C_6H_{12}O_6$, and indoxyl,



Indoxyl, in alkaline solution, is readily oxidized by the air to indigo.

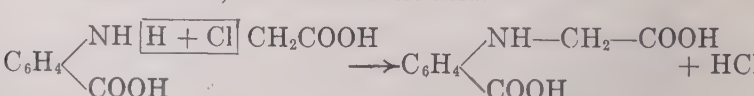


Indoxyl Indigo

The commercial method of preparing the dye from natural sources consists of leaching the leaves of the plant with lukewarm water, rendering the aqueous extract alkaline by the addition of limewater and churning the alkaline solution with paddle wheels to aërate and thus oxidize it. Extraction with boiling water yields the unhydrolyzed glucoside, for the activity of the enzyme is destroyed at that temperature.

Since 1900, the dye has been produced synthetically, and thousands of acres of land in India, Japan, and South America, formerly devoted to the production of indigo plants, are now cultivated for the production of other crops.

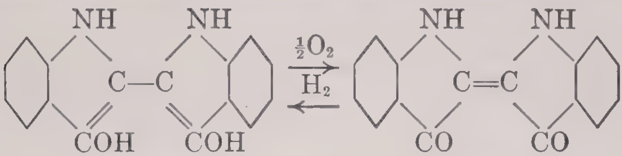
The first successful commercial synthesis of indigo was accomplished by a reaction between anthranilic acid (ortho aminobenzoic acid) and chloracetic acid.



The product formed (phenylglycine-*o*-carboxylic acid) when fused with sodium hydroxide yields indoxyl, carbon dioxide, and water. The indoxyl is changed to indigo, as indicated above.

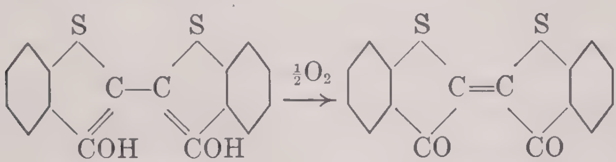
Indigo is reduced in an alkaline solution of calcium hyposulphite (CaS_2O_4) and by other reducing agents with the

production of a colorless soluble product known as indigo white. Textiles are soaked in solutions of indigo white, then exposed to the air. The color develops in the fibers of the cloth through atmospheric oxidation during the process of drying. Deep shades are produced by repeating the operation several times.



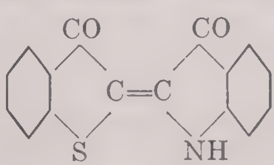
Indigo white — Indigo

Thioindigo is made from thiosalicylic acid and chloracetic acid by reactions analogous to those given for the production of indigo. It is reduced to a colorless, soluble compound, known as thioindigo white, which is changed by atmospheric oxidation to an insoluble red dye.



Thioindigo white — Thioindigo

Ciba violet is a representative of a group of dyes in which half the molecule is constituted like indigo and half like thioindigo. It is a vat dye, developing a color between the red of thioindigo and the blue of indigo. It has the structure:



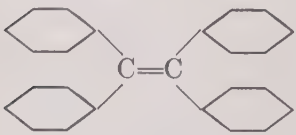
STRUCTURE AND COLOR

The indigoid dyes are characterized by the group >C=C< between various types of condensed rings. The azo dyes have the group —N=N— between aromatic radicals. Each triphenylmethane dye has a benzene nucleus in the quinoid form, . These groups were classified by Witt* as

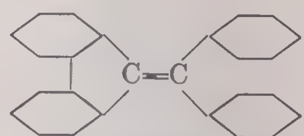
* O. N. Witt, *Ber.*, **21**, 325 (1888).

chromophores (color producers). To this list should be added the groups $—NO_2$, $—NO$, $—\overset{O}{\widehat{N—N}}—$, and $—CO—CO—$.

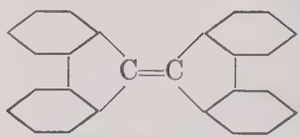
The group $>C{=}C<$ is only potentially a chromophore. Many colorless compounds possess this group. Condensed cyclic nuclei in connection with the ethylene group usually produce colored bodies, as shown in the structures of the indigoids. An example of the result of condensing, or tying together, aromatic nuclei is found in the following derivatives of ethylene.



Tetraphenylethylene
(colorless)



Diphenylene-diphenylethylene
(colorless — yellow in solution)



Bidiphenylene-ethylene
(red crystals — red in solution)

The stereo-chemical structure of the molecule is another factor that influences the absorption of light. We have, for example, a colored and a colorless dibenzoylethylene. They are geometrical isomers.

$$\begin{array}{c} H \cdot C \cdot CO \cdot C_6H_5 \\ \| \\ H \cdot C \cdot CO \cdot C_6H_5 \\ \text{Colorless} \end{array} \qquad \begin{array}{r} H \cdot C \cdot CO \cdot C_6H_5 \\ \| \qquad\qquad \\ C_6H_5 \cdot CO \cdot C \cdot H \qquad \\ \text{Yellow} \qquad \end{array}$$

Two carbonyl groups, if adjacent, impart color to the molecule; but if separated by one or more carbon atoms, this property disappears.

$CH_3 \cdot CO \cdot CO \cdot CH_3$
Diacetyl (yellow)

$CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$
Acetyl acetone (colorless)

$C_6H_5 \cdot CO \cdot CO \cdot C_6H_5$
Benzil (yellow)

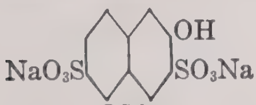
$C_6H_5 \cdot CO \cdot CH_2 \cdot CO \cdot C_6H_5$
Benzoyl acetophenone (colorless)

If in addition to a chromophore the compound possesses an amino or a hydroxyl group in an aromatic residue, it is not only colored but it is a dye. That is to say, it is capable of

imparting a more or less permanent color to textile fibers. A group that modifies the properties of a colored compound in such a way as to make it a dye is called an auxochrome group. Azobenzene is colored, but it fails to dye textiles. Aminoazobenzene and hydroxyazobenzene are yellow dyes.

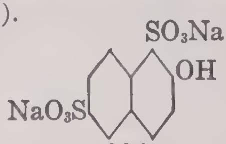
To produce a red azo dye, at least one of the groups attached to the diazo nitrogen atoms must be heavier than a phenyl radical, as, for example, a naphthol or naphthylamine residue. Nearly all of the aliphatic azo-compounds are colored liquids. They are not dyes.

The trade names, *R-salt* and *G-salt*, are applied to the naphthol disulphonic acids, to indicate that these naphthol derivatives couple with diazonium salts to form pure red and yellowish red dyes, respectively (Rot and Gelb).



R-Salt

and



G-Salt

The auxochrome may, also, contribute to the determination of color or shade. Naphthylaminesulphonic acid and benzidine yield a pure red, whereas, naphtholsulphonic acid and benzidine yield a reddish blue dye.

With one amino group para to the methane carbon in triphenylmethane we have an orange-red dye. With two rings so modified the color changes to violet, and with an amino group in the para position in each of the three benzene rings we have the bluish red pararosaniline. By substituting four methyl radicals for hydrogen atoms of the amino groups in pararosaniline, we obtain malachite green. When six methyl groups are substituted for the six amino hydrogen atoms in pararosaniline, crystal violet is produced. The substitution of two amino hydrogen atoms in pararosaniline by phenyl radicals changes the color to violet; and the introduction of three phenyl radicals gives a blue dye.

Theory of color. There must be some fundamental property of matter that makes possible the development of color, and it must be a property that is dependent upon molecular structure and sensitive to slight changes in configuration — a property that makes possible a gradual and continuous shift from one end to the other of the visible spectrum, through slight

modifications of the molecule, either by addition or substitution, or through intramolecular rearrangement.

G. N. Lewis has offered a satisfactory explanation of the origin of color. According to his theory, color is the result of the partial absorption of light waves by valence electrons. In compounds possessing the so-called chromophore groups, certain electrons are supposed to be vibrating with frequencies corresponding to the frequencies of light in the visible spectrum. If these electrons absorb the light of short wave length (blue and violet), the compound displays the complementary colors (yellow and greenish yellow). If the electron is held less rigidly and, therefore, vibrates more slowly, so that its period synchronates with the period of yellow light, the color of the compound approaches that of the violet end of the spectrum.

An analogy is found in the selective absorption of sound waves. When sound is produced by striking simultaneously several keys of a piano, it is often observed that a tuning fork or a string of another instrument, having the same period of oscillation as one of the notes struck, absorbs part of the energy of the sound wave and is set in motion. The tuning fork acts analytically, absorbing the energy of vibrations of one definite frequency, and allowing all other components of the mixture to pass unchanged. It would be possible to interpose between the piano and the auditor a sufficient number of strings or tuning forks, all having the same frequency, to act as a complete screen for a particular pitch, without appreciably diminishing the intensity of other notes simultaneously produced.

In a similar way the components of white light suffer selective absorption by electrons of the compounds that appear colored. The analogy is not quite complete, for in the absorption of light waves the energy is taken up only by electrically charged particles.

Atoms have two types of charged particles, namely, the nuclei and the electrons. The positive nucleus of an atom has a mass almost equal to the entire atomic mass, and, in all probability, such heavy bodies do not vibrate with the frequency of visible light. On the other hand, electrons must vibrate with extremely high frequencies, generally absorbing radiant energy in the ultra violet only. Hence, most compounds are colorless. If, through the establishment of a particular molecular structure, the rate of vibration of an electron is made to

diminish, absorption may occur in the region of the visible spectrum, and if this happens, color is developed.

The establishment of a double bond in a molecule tends to weaken the forces acting between nuclei and electrons, for if a valence bond consists of a pair of electrons between nuclei, a double bond consists of two such pairs, and it is certain that both pairs cannot occupy positions of maximum stability. The enhanced reactivity of unsaturated compounds is due to greater freedom of the electrons constituting the double bond. The typical chromophore groups contain one or more double bonds.

Free radicals are colored. Ethane is a very stable compound. It displays no tendency to dissociate into methyl radicals. By substituting heavy groups for hydrogen atoms in ethane the bond between the carbon atoms is weakened to such an extent that dissociation actually occurs and free radicals are obtained. Each radical possesses an unpaired or odd electron held more loosely than any of the electrons actually functioning as valence electrons (the dissociation depends upon such loosening effect), and, as would be expected from this theory, the free radicals are generally colored. Of all the free radicals discovered up to the present time only one (namely, nitric oxide) is colorless. It is not necessary actually to break the bond between atoms to produce color; any change in environment that weakens the bond may loosen electrons sufficiently to change a colorless into a colored body.

The theory was stated by Lewis as follows:*

> When a particle is held in position by definite constraints, it is capable of vibrating with a definite frequency, and this frequency is determined solely by the magnitude of the constraints and by the mass of the particle. When such a particle is electrically charged and subjected to the alternating electromagnetic forces which constitute a beam of light, and when the frequency of the light is near to the characteristic frequency of the particle, the latter is set to vibrating and through frictional processes the energy of the light is absorbed.
>
> The two kinds of charged particles which exist in chemical substances are charged atoms and electrons. The former, on account of their relatively large mass, have low characteristic frequencies which are far below the frequencies of visible light and therefore cause absorption only in the ultra-red spectrum. The electrons, on the other hand, because of their small mass and the rigid constraints by which they are ordinarily bound, usually have frequencies higher than those of visible light and therefore absorb light

* G. N. Lewis, *Am. Chem. Soc.*, 38, 783 (1916).

only in the ultra-violet. The majority of substances, therefore, show no special absorption of visible light and are therefore colorless.

When, however, either by a change in the constitution of the molecule or through a change in the environment, the constraints acting upon an electron become weaker, the frequency of that electron becomes less. It may then begin to absorb visible light of the highest frequency, namely, the violet and blue, and the transmitted light is therefore yellow. Whenever a colorless substance becomes colored, through slight changes by substitution of somewhat different groups within the molecule, or by gradual change in the environment, the substance is always yellow. But if the changes are made more pronounced and the characteristic frequency of the electron or electrons concerned is still further lowered, so that the maximum of absorption is in some other part of the visible spectrum, different colors will be produced, and ultimately when the electron is nearly freed from constraint, as in the case of an alkali metal dissolved in liquid ammonia, the maximum of absorption is in the ultra-red and red, and a blue color results.

Now colored substances are the very ones in which, according to our theory, the electrons are least firmly held. Thus such substances as nitrogen dioxide and sodium vapor, which contain an uneven number of electrons and which therefore hold one of the electrons very loosely, are colored. If, however, sodium combines with chlorine, the electron becomes firmly held by the latter element, and when nitrogen dioxide combines even with itself to form N_2O_4, the electron is again firmly held and the color disappears. . . . .

Turning now to substances containing an even number of electrons, we see in the case of the halogens how the intensity and character of the color vary with the polar character. Thus the electrons which are concerned in the union of the two atoms of iodine are held by weaker constraints than in the case of bromine, and so on through the group. The electrons in fluorine, being most firmly held, absorb only the extreme violet end of the visible spectrum.

In general, color and a high degree of polarity go hand in hand, as is abundantly shown in the great class of organic dyes. Both of these phenomena are due to the same cause, namely, the weakness of the constraints acting upon one or more electrons.

It has frequently been noticed that there is a striking parallelism between color and the possibility of tautomeric change, and it has been assumed by some that color is in some way due to an alternation between two extreme tautomeric forms. But this is not precisely the case. When electrons are sufficiently free to produce absorption in the visible spectrum, that part of the molecule in which they are will always be highly polar and reactive, and there will be opportunity for free transition from one limiting form to another. Thus if a tautomeric process consists chiefly in the movement of electrons, there will be electrons in some molecules which are hung by loose constraints between the two extreme forms, and these are the electrons which will have a sufficiently low characteristic frequency to produce color.

THE ALKALOIDS

The term alkaloid has been applied to any basic substance of vegetable origin which contains nitrogen in a heterocyclic ring. This definition of the term is too broad. It brings into the alkaloid group many compounds that, from a chemical point of view, are in no way related to each other. But attempts to classify the alkaloids on the basis of structure have been unsuccessful, and, with some reservations, this vague definition is still used. It is doubtful whether the purine bodies, caffeine, theobromine, and related substances, should be called alkaloids, yet they are plant products sufficiently basic to form salts with strong acids, and they have nitrogen-carbon ring structures.

Most of the typical alkaloids are derivatives of pyridine or quinoline, but to define them as such derivatives would exclude morphine, the most important member of the group, the first one isolated, and the one to which the name was first applied. Oxazine, pyrrolidine, and several other types of rings are found in some alkaloids.

More than two hundred vegetable bases have been isolated, analyzed, and described. The structures of many of them have been determined. Some of them have been produced synthetically.

An acquaintance with pyridine and quinoline and some of their derivatives is a prerequisite to the study of the alkaloids.

PYRIDINE AND QUINOLINE

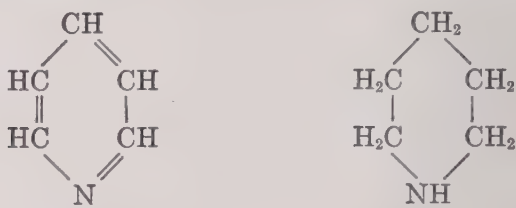
Pyridine, C_5H_5N, is a colorless liquid, possessing a persistent and disagreeable odor. It boils at 115°; dissolves in all proportions in water, alcohol, and ether. It is obtained from bones by dry distillation, from coal tar, and from crude petroleum. It is obtained from nicotine and from quinine when these alkaloids are heated with zinc dust.

Pyridine is a tertiary base which is easily reduced by sodium amalgam to a secondary amine known as piperidine. At high

temperatures it is reduced by hydriodic acid to ammonia and normal pentane.

Pyridine is a very stable compound. Oxidizing agents such as chromic acid, potassium permanganate, and concentrated nitric acid do not attack it. At 300° concentrated sulphuric acid acts upon it slowly, forming a β-monosulphonic acid.

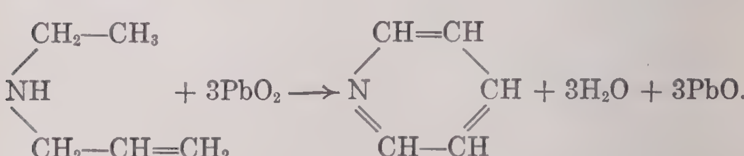
The structure of pyridine corresponds to benzene in which one CH group has been replaced by nitrogen. It exhibits the same state of unsaturation as does benzene. The reduction product, piperidine, referred to above, is a saturated cyclic compound.



Pyridine Piperidine

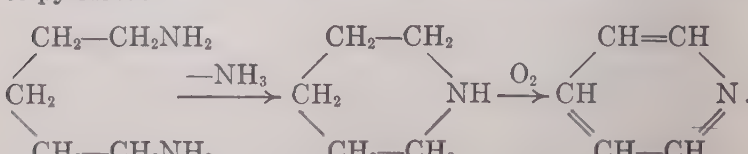
Pyridine may be prepared by the following methods:

1. The oxidation of ethylallylamine by lead peroxide at 450° to 500°:



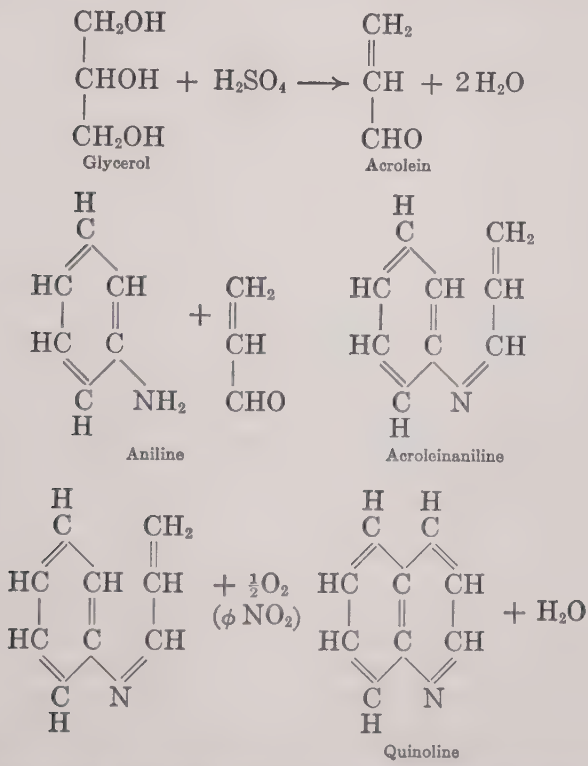
2. By passing acetylene and hydrogen cyanide or alcohol vapor and ammonia through a tube heated to dull redness. The yield is poor.

3. Pentamethylenediamine when heated yields ammonia and piperidine. The latter is easily oxidized by nitrobenzene to pyridine:

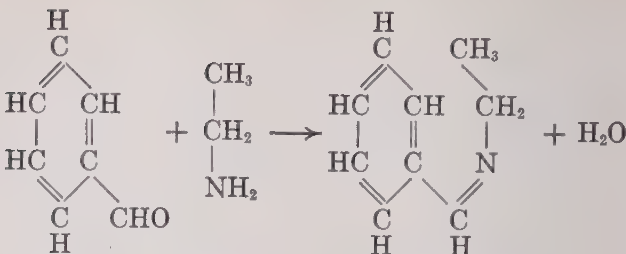


Pentamethylenediamine Piperidine Pyridine

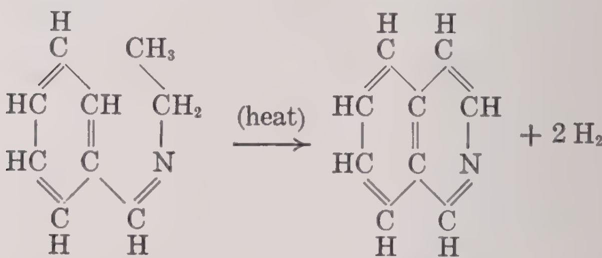
Quinoline, a colorless, hygroscopic liquid boiling at 239°, is a tertiary base. Like pyridine it forms quaternary salts by addition of alkyl halides or halogen acids. It bears the same relation to naphthalene that pyridine does to benzene. Skraup synthesized quinoline by heating a mixture of aniline, glycerine, sulphuric acid, and nitrobenzene. The glycerine is dehydrated by sulphuric acid, acrolein being the chief product. Acrolein undergoes the usual aldehyde condensation with aniline, and nitrobenzene oxidizes the condensation product, with the formation of quinoline. The various steps are indicated below:



Isoquinoline is isomeric with quinoline and has very similar properties. Structurally it differs from quinoline only in the position of the nitrogen atom. It has been synthesized by condensing benzaldehyde with ethylamine and heating the vapor of the condensation product:



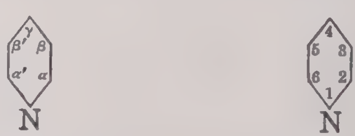
Benzaldehyde Ethylamine Benzylidine-ethylamine



Isoquinoline

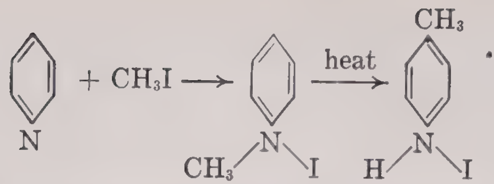
Many other methods have been devised for synthesizing pyridine, quinoline, and isoquinoline.*

The introduction of nitrogen into the ring makes the possible number of isomeric substituted pyridines much greater than the number of corresponding benzene derivatives. Thus there are three mono-substituted pyridines and six di-substitution products. The positions in the ring are indicated by the letters of the Greek alphabet or by numbers:



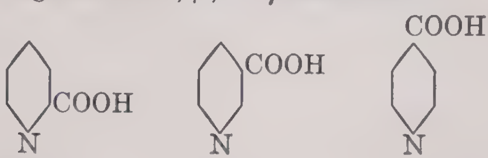
Quaternary salts of pyridine are formed by direct addition of alkyl halides. When heated to 300°, these compounds undergo rearrangement corresponding to the shift of alkyl radicals from nitrogen to carbon in quaternary derivatives of aniline and other aromatic amines. These reactions may be represented as follows:

* For other methods and for details of syntheses outlined above, see The Vegetable Alkaloids, Pictet, trans. by Biddle.



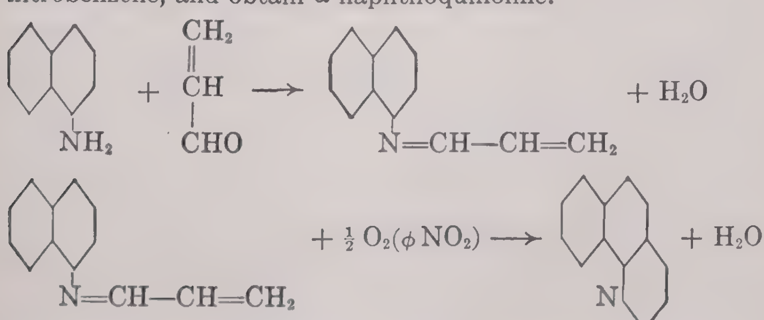
α-Substitution occurs to some extent at the same time. The free methyl pyridine is obtained by distilling the hydriodide with an alkali. A β-sulphonic acid is formed when pyridine is heated to 300° in a sealed tube with concentrated sulphuric acid.

Three monocarboxylic acids of pyridine are known, and according to the structure theory only three are possible. They are produced when certain alkaloids are subjected to oxidation, or they may be synthesized by oxidizing substances that have the pyridine ring with an α, β, or γ side chain:



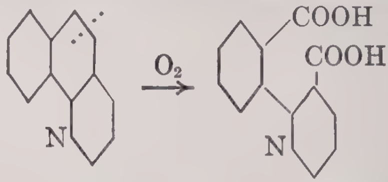
Picolinic acid (m.p. 137°) Nicotinic acid (m.p. 229°) Isonicotinic acid (m.p. 306°)

The structures of these acids have been proved by synthetic methods. For example, applying the principle of Skraup's synthesis of quinoline, we may condense α-naphthylamine with acrolein in the presence of a mild oxidizing agent, such as nitrobenzene, and obtain α-naphthoquinoline.

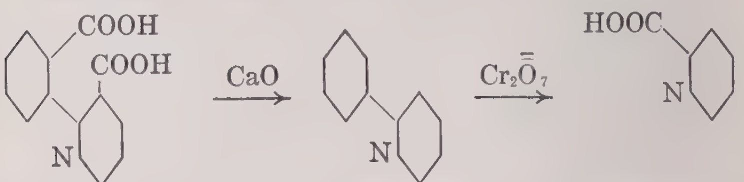


By oxidation it is possible to convert this product into a dicarboxylic acid without loss of carbon. There is only one position in the molecule where, by oxidation, two carboxyl groups could

be formed without producing an acid with fewer carbon atoms. The position is indicated by the dotted line below:

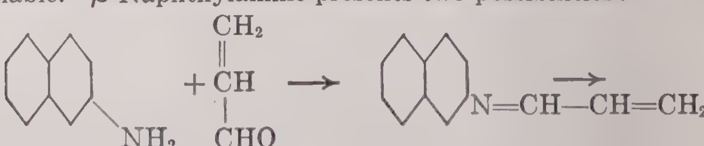


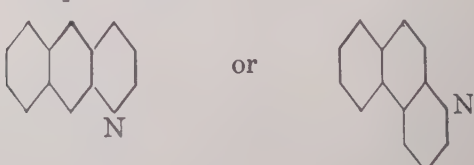
The carboxyl groups are replaced by hydrogen when the acid is distilled with lime and the resulting α-phenylpyridine is converted by chromic acid into picolinic acid:



Phenyl-pyridine dicarboxylic acid Phenylpyridine Picolinic acid

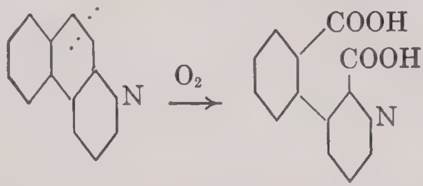
The constitution of nicotinic acid may be determined in a similar way. Acrolein combines with β-naphthylamine as it does with aniline or α-naphthylamine. The condensation product is oxidized by nitrobenzene, forming a pyridine ring by attachment of the terminal carbon atom of the acrolein residue to a carbon atom ortho to the nitrogen of the aromatic amine. In Skraup's synthesis of quinoline, it makes no difference which of the two positions ortho to the amino group is involved in the formation of the pyridine ring. When acrolein is condensed with α-naphthylamine, as in the case referred to in the synthesis of picolinic acid, only one position ortho to the amino group is available. β-Naphthylamine presents two possibilities:



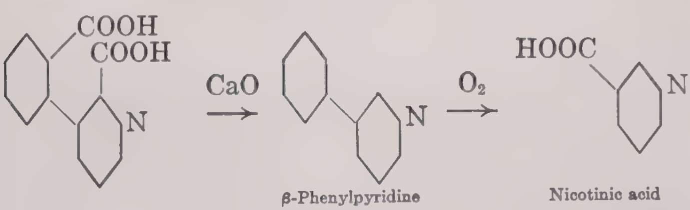


I II

The product actually formed can be converted into a dicarboxylic acid without loss of carbon. There is no possibility of oxidizing formula I so as to produce a dicarboxylic acid, without at the same time reducing the number of carbon atoms in the molecule, and formula II presents only one such possibility, as indicated below:



The carboxyl groups are removed by distillation with lime, and the remaining phenyl radical is replaced by carboxyl through the agency of chromic acid. The superior stability of the pyridine ring is shown in these reactions. It is the benzene residue that suffers oxidation, yielding in this case nicotinic acid rather than benzoic acid:



CONIINE

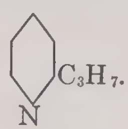
Coniine, $C_8H_{17}N$, a colorless liquid (b.p. 166°, sp. gr. 0.845), is the principal alkaloid in hemlock. The poisonous character of an extract of hemlock was known before the dawn of the Christian era. Socrates was compelled to terminate his life by means of this substance. The fatal dose is from 0.1 to 0.2 grams. There is no satisfactory antidote.

The free base was first isolated by Geiger in 1831, and synthesized by Ladenburg fifty years later. It was the first alkaloid to be made by artificial methods. The constitution of the compound was determined by Hofmann through an interpretation of the following changes.

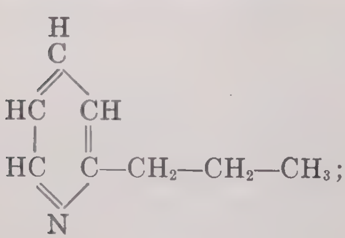
When coniine is distilled over zinc dust, it gives rise to free hydrogen and a compound known as conyrine, having the empirical formula, $C_8H_{11}N$:

$$\underset{\text{Coniine}}{C_8H_{17}N} \longrightarrow \underset{\text{Conyrine}}{C_8H_{11}N} + 3H_2.$$

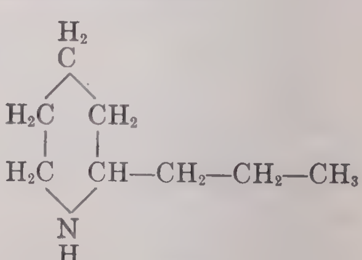
Conyrine is readily oxidized to picolinic acid, which differs from conyrine by $C_2H_6O_2$. The two oxygen atoms are introduced by the oxidizing agent in forming the carboxyl group, — conyrine itself contains no oxygen. The loss of carbon and hydrogen in the oxidation process amounts, therefore, to C_2H_6. Since picolinic acid has only one carboxyl group, it is evident that conyrine is a derivative of pyridine with one and only one side chain. The side chain must be in the α-position, since in picolinic acid the carboxyl group occupies this position. The composition of the side chain must be C_3H_7. It is C_2H_6 plus the carbon and hydrogen retained in the carboxyl group.

The formula may be written 

The question as to whether the side chain is normal-propyl or iso-propyl was settled by subjecting conyrine to the action of hydroidic acid at 300° C. It was reduced to normal octane and ammonia. Conyrine is, therefore, normal propylpyridine, and coniine, having six more hydrogen atoms, is the corresponding saturated compound, *n*-propylpiperidine:



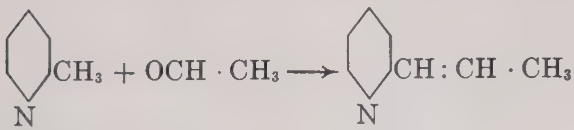
Conyrine



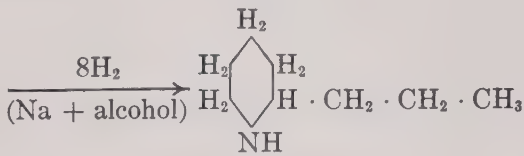
Coniine

All syntheses of coniine lend support to the conclusion that it has this structure. The simplest and most direct synthesis is accomplished by condensing α-methylpyridine (picoline) with

acetaldehyde, in the presence of zinc chloride, and reducing the condensation product:



Picoline (b.p. 129°) Acetaldehyde Allylpyridine (b.p. 190°)



Coniine (b.p. 166°)

The racemic mixture, produced by this synthesis, was resolved by Ladenburg into the optically active forms, by fractional distillation of the coniine tartrates. The dextro-rotatory modification and coniine derived from hemlock were found to be identical.

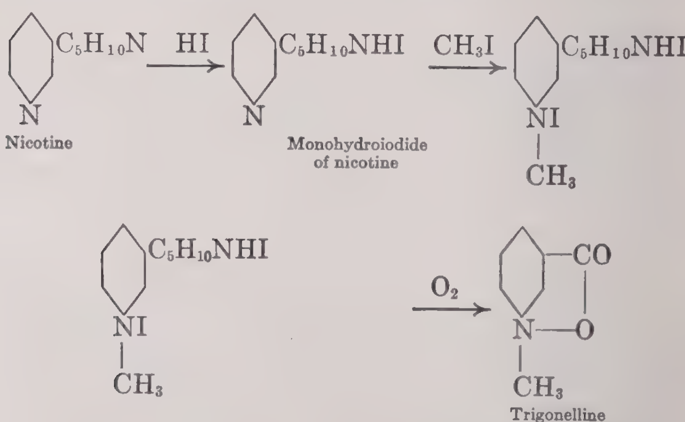
NICOTINE

Nicotine, $C_{10}H_{14}N_2$, when pure, is a colorless, odorless liquid. It acquires a brown color and a tobacco odor on standing. It is fully as poisonous as hydrocyanic acid and about ten times as poisonous as coniine. It has an alkaline reaction, produces a burning sensation in the mouth, causes profuse salivation, and to some extent increases the flow of all secretions. Acute nicotine poisoning gives rise to mental confusion, vomiting, and finally convulsions.

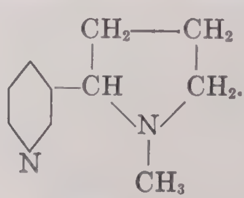
Nicotine occurs in the leaves of the tobacco plant principally in the form of salts of malic and citric acids. The tobacco plant is the chief source of this alkaloid. The plant is indigenous to America and was unknown in Europe until 1650. Tobacco is now used in every country in the world. Its use is made possible by the fact that only exceedingly small quantities of nicotine are introduced into the system in the practice of smoking. The component of tobacco that acts as a habit-forming drug has not been discovered. It is not nicotine.

Nitric acid converts nicotine into nicotinic acid. The alkaloid is therefore a pyridine derivative, and the side chain, $C_5H_{10}N$, is in the β-position. Nicotine is a di-tertiary

base, yielding, with methyl iodide, two different quaternary salts. Each nitrogen atom, therefore, is linked by three valences to carbon. The nitrogen of the pyridine ring is less basic than the one in the $C_5H_{10}N$ group; for when the monohydroiodide is treated with methyl iodide and then oxidized with potassium permanganate, trigonelline is formed — a compound known to have a methyl group on the pyridine nitrogen. In forming the monohydroiodide it is evident that the hydrogen iodide entered into combination with the nitrogen of the $C_5H_{10}N$ group, leaving the nitrogen of the pyridine ring free. On further treatment with methyl iodide or hydrogen iodide the pyridine nitrogen also is called into play:



The monohydroiodide when heated yields methyl amine. The group $C_5H_{10}N$ must, therefore, contain a methyl group attached to the nitrogen. On the basis of these and other considerations the following structure is assigned to nicotine:



Nicotine

Pictet confirmed this constitution of the alkaloid by synthesizing β-methylpyrrolidine-pyridine and resolving it into its

enantiomorphic forms. The lævo-rotatory compound proved to be nicotine.

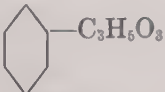
ATROPINE AND BELLADONNA

Atropine, $C_{17}H_{23}NO_3$, and belladonna, $C_{17}H_{21}NO_2$, are the principal alkaloids of the nightshade. They occur together usually, and produce similar physiological effects. Distinct symptoms of poisoning follow the ingestion of quantities as small as 0.006 of a gram of either of these alkaloids, and 0.05 of a gram constitutes a fatal dose.

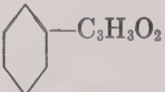
The symptoms are extreme thirst, inability to swallow, hoarseness, and headache. The pupils of the eyes are enlarged, and vision is indistinct. In the last stages violent types of delirium and convulsions are common. Respiration is arrested during the spasms, and in many cases death has resulted from asphyxia. Frequent administration of very small doses deranges the mind, producing insanity. These alkaloids are useful in optic surgery. They act as local anæsthetics, paralyzing the nerves controlling the muscles of the eye. At the same time they cause dilation of the pupil.

In composition, atropine and belladonna differ by two atoms of hydrogen and one of oxygen. Both are esters. When hydrolyzed, atropine yields tropic acid and an alcohol called tropine. Belladonna yields atropic acid and tropine. In order to establish the constitutional formulas of these alkaloids, it is necessary to determine the structures of tropic acid, atropic acid, and tropine.

Tropic acid has the empirical formula $C_9H_{10}O_3$. Atropic acid is $C_9H_8O_2$. Both are converted into benzoic acid by oxidation. Each may, therefore, be represented by a benzene ring with one side chain.



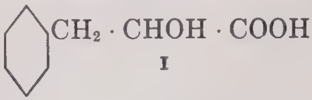
Tropic acid



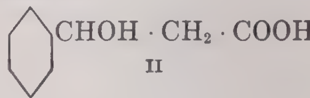
Atropic acid

They are monobasic acids, hence each has a carboxyl group in the side chain. Tropic acid has a hydroxyl group also, for it forms an acetyl derivative with acetic anhydride. There are four possible structures for a benzene ring with one side chain — the side chain having the composition $C_3H_5O_3$ and possessing

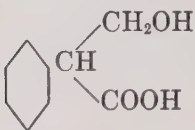
one carboxyl and one hydroxyl group. One of these structures must represent the tropic acid molecule:



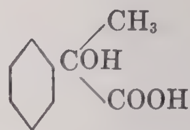
I



II

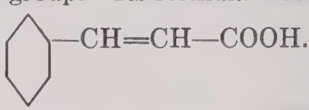


III

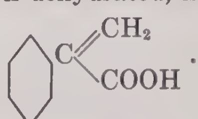


IV

When tropic acid is heated, it loses water and forms atropic acid. Atropic acid has no alcoholic hydroxyl group. It is unsaturated and forms an addition product with bromine. Formulas I and II would yield the same product if water were eliminated and a double bond established with removal of the alcoholic hydroxyl group. Its formula would necessarily be



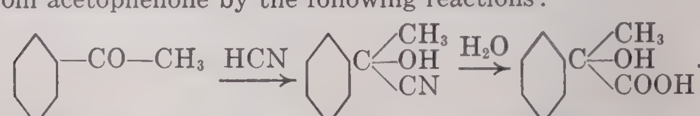
But this is cinnamic acid, not atropic. Therefore tropic acid is not represented by I nor by II. Formulas III and IV would yield the same product if dehydrated, namely:



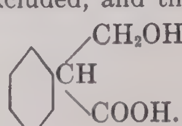
Atropic acid

This product is, therefore, atropic acid, and tropic acid is either III or IV.

A compound having formula IV has been made synthetically from acetophenone by the following reactions:



This product is not tropic acid; it is known as atrolactic acid. Formula IV is thus excluded, and the only possible structure for tropic acid is



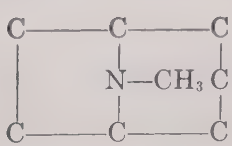
Tropine, $C_8H_{15}NO$, crystallizes in colorless plates (m.p. 63°, b.p. 233°). It is a strong tertiary base, hygroscopic, and optically inactive. It forms esters with acids and with acid chlorides, hence its oxygen atom is in a hydroxyl group. When distilled with barium oxide, it yields water, methyl amine, and tropilidine (C_7H_8). The latter is a seven-membered ring compound, a cycloheptatriene. The production of methyl amine indicates that in tropine there is a methyl group attached to the nitrogen atom, and since it is a tertiary base, the nitrogen must be attached to carbon by two other bonds also. When heated to 220° with sulphuric acid, tropine yields an unsaturated tertiary base, tropidine, containing no oxygen:

$$\underset{\text{Tropine}}{C_8H_{15}NO} \longrightarrow \underset{\text{Tropidine}}{C_8H_{13}N} + H_2O.$$

Tropidine is reduced by hot hydriodic acid to normal heptane and methyl amine, indicating its possession of a structure, capable of yielding an unbranched chain of seven carbon atoms, when the nitrogen and its attached methyl group are removed.

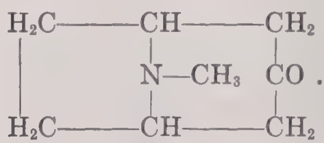
Methyl pyridine and methyl pyrrolidine have been identified among the products obtained from tropine by distillation with zinc dust. We have, therefore, in tropine, a continuous chain of seven carbon atoms, and a nitrogen atom attached to a methyl group and to two other carbon atoms. The nitrogen atom is a member of a pyridine ring and at the same time a member of a pyrrolidine ring.

The skeleton of the tropine molecule must, therefore, appear as follows:



When tropine is oxidized with potassium permanganate or lead dioxide, a ketone, tropinone, is formed, differing from tropine by two hydrogen atoms. The hydroxyl group is therefore in a secondary alcohol group, CHOH, and this group is in the pyridine ring; for when the hydroxyl group is replaced by bromine, and the compound is heated, methylbrompyridine is formed. Similar evidence is obtained by dehydrating tropine by

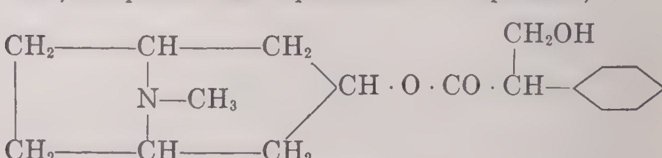
means of hot sulphuric acid. The hydroxyl group is removed with hydrogen from an adjacent carbon. The unsaturated product formed, namely, tropidine, $C_8H_{13}N$, absorbs bromine, yielding tropidine dibromide, $C_8H_{13}NBr_2$, which decomposes at 180° with the formation of dibrommethylpyridine. Conversion of a secondary alcohol into a ketone enhances the activity of hydrogen on carbon atoms adjacent to the carbonyl group. Consideration of this fact led Wilstätter to the conclusion that the carbonyl is between two methylene (CH_2) groups, for tropinone reacts with nitrous acid yielding a diisonitroso-derivative; with benzaldehyde, giving a dibenzal-derivative; and with benzenediazonium chloride, forming a product containing two phenylhydrazine residues. The following structure accounts for these properties:



Tropinone

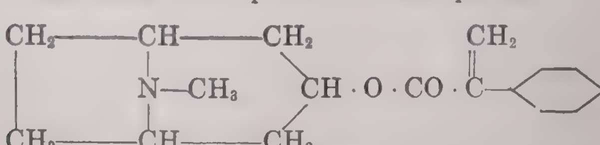
It is a ring system including piperidine, pyrrolidine, and heptamethylene nuclei. The structure accounts for the formation of methylamine and heptane on reduction, the production of pyridine derivatives when oxidized with bromine, the formation of tropidine by elimination of water, and all other properties of the base. Tropine is the corresponding secondary alcohol.

Now, atropine is the tropine ester of tropic acid,



Atropine

and belladonna is the tropine ester of atropic acid.

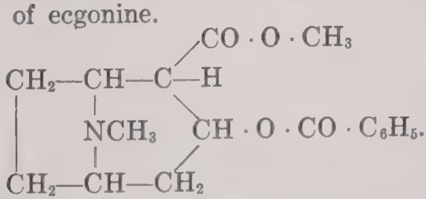


Belladonna

COCAINE

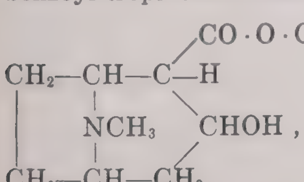
Cocaine, $C_{17}H_{21}NO_4$, is a white crystalline solid melting at 98°. It is extracted from coca leaves (not cocoa). It has a bitter taste, an alkaline reaction, and is lævo-rotatory. It has been used extensively as a local anæsthetic, but it is being supplanted by the less harmful novocaine — a synthetic product not related to the alkaloids. Cocaine is a poison, but it requires a large dose (nearly one gram) to cause death in man. Small doses cause restlessness and irritability with quickened pulse. It is used in very small amounts habitually by some individuals who claim that it acts as a tonic, overcoming fatigue and sensations of hunger. Many workmen in the Andes chew the coca leaves, believing that they derive therefrom unusual power of endurance; and some South American travelers claim to have experienced remarkable rejuvenation under the influence of cocaine. These claims have not been confirmed by experiments in less romantic quarters. In mydriatic properties cocaine resembles atropine. Like atropine, also, its continued use results in mental aberrations and insanity.

On hydrolysis cocaine yields ecgonine, methyl alcohol, and benzoic acid. Ecgonine is a carboxylic derivative of tropine. Cocaine is produced by the action of benzoyl chloride on the methyl ester of ecgonine.

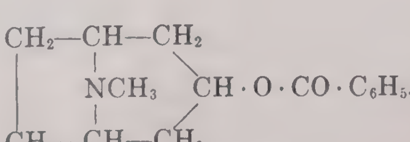


Cocaine

The effects produced upon the sensory nerves by this alkaloid have been traced to the reciprocal relations of the tropine, benzoyl, and methyoxy groups. Thus methyl-ecgonine and benzoyl-tropine are inactive:

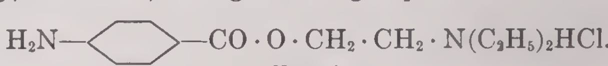


Methyl-ecgonine



Benzoyl-tropine

With both ester groups in the same molecule the anæsthetic property appears. Other aliphatic radicals may be substituted for the methyl group without destroying the physiological activity of the substance; but substitution of other radicals for the benzoic acid residue lessens or destroys its activity. This fact has led to the investigation of many benzoic acid derivatives, and some of them have proved to be capable of producing local anæsthesia. The most successful substitute for cocaine, namely, novocaine, belongs to this group: *



Novocaine

The free base of novocaine (or of procaine) is insoluble in water. It dissolves readily in oils and in benzene, alcohol, or chloroform. The hydrochloride is soluble in water.

STRYCHNINE

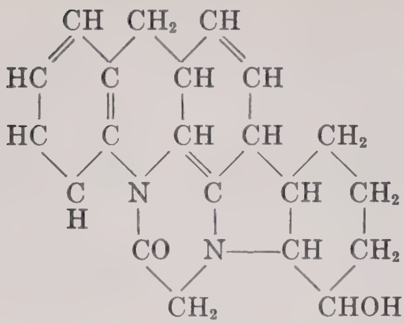
Strychnine, $C_{21}H_{22}N_2O_2$, occurs with brucine, $C_{23}H_{26}N_2O_4$, in the nuts or seeds, leaves, and bark of the plants of the genus strychnos. Nux vomica, the seed of *Strychnos nux vomica*, contains more than one per cent of strychnine and as much brucine. Curare, a resin extracted from many species of strychnos trees, contains strychnine, brucine, curarine, and several other related poisonous bases.

Strychnine crystallizes in prisms (m.p. 269°) which are soluble in alcohol and practically insoluble in water. † It is lævo-rotatory, has an alkaline reaction and a bitter taste.

The structure of the strychnine molecule has not been determined. Quinoline and indol have been isolated from the decomposition products obtained by fusing the alkaloid with caustic potash, and pyridine has been obtained from it by distillation with lime. It possesses a carbonyl group, an alcoholic hydroxyl group, a reduced benzene ring, a quinoline residue, and an indol group; and from these considerations Perkins and Robinson have proposed the formula given below. This structure accounts for the reactions of strychnine, but until it is confirmed by actual synthesis it must be regarded as tentative only:

* For a discussion of compounds related to novocaine see Meyer and Gottlieb, Pharmacology.

† Strychnine salts are soluble in water. The sulphate is generally used.



Strychnine displays a selective action on the reflex arcs of the central nervous system. Instead of obtaining normally coördinated movements, in response to definite stimuli, every stimulus affecting the sensory organs of a victim of strychnine poisoning causes simultaneous contractions of all the skeletal muscles. These tetanic convulsions may last for a few seconds or for several minutes. Since the respiratory muscles are involved in the tonic contractions, symptoms of asphyxia often appear. After several convulsions paralysis develops and death results from exhaustion of the nervous system. The lethal dose is about 0.1 gram. The patient suffers great pain due to the violent contractions of the muscles. He retains consciousness and realizes his condition, the mind being active and unclouded to the last.

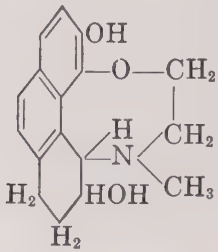
MORPHINE

The dried sap of some species of poppies constitutes a waxlike substance known as opium. It is a mixture of gums, resins, carbohydrates, fats, proteins, salts, and alkaloids. The chief representative of the group of vegetable bases in opium is morphine, $C_{17}H_{19}NO_3$.

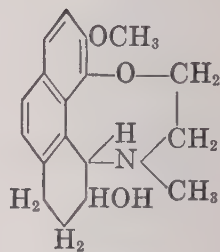
Morphine is a colorless, crystalline base which melts and decomposes at 247°. It is only slightly soluble in water, benzene, chloroform, and ether, but it dissolves readily in alcohol. Its solutions are alkaline, bitter, and lævo-rotatory.

The constitution of morphine has not been fully established. It is a tertiary base with a methyl group attached to the nitrogen. It is a phenanthrene derivative, a phenol and an ether. Its reactions, as well as its composition and molecular weight, are in accord with the following structure, but confirmation by

synthesis is yet to be accomplished. Codeine is a methyl ether of morphine.



Morphine



Codeine

The quantity of codeine in opium is usually less than 0.5 per cent, whereas morphine constitutes from 6 per cent to 10 per cent of the substance. Twenty different alkaloids have been identified as components of opium, but with the exception of morphine, narcotine, papaverine, thebaine and codeine they are present in mere traces.

Morphine produces a variety of effects in various species of animals. In human beings it acts as a sedative, small doses causing sleep and toxic doses producing profound unconsciousness. Its most important therapeutic use is that of relieving pain, which is accomplished in most cases by administration of less than 0.01 of a gram. The ability to perceive pain is depressed by doses much too small to cause sleep. In this respect morphine differs from chloroform.

Although no other drug stands in the same class with morphine in respect to relieving pain, its use must be carefully curtailed on account of the fact that it carries with it a strong desire to repeat the treatment even when entirely free from pain. It is the most powerful habit-forming drug known.*

Acute morphine poisoning is caused by doses ranging from 0.03 to 0.06 of a gram. The average lethal dose for an adult unaccustomed to its use is about 0.35 of a gram. The system acquires tolerance for morphine and habitual users take large doses with impunity. The effects described above are produced by much smaller quantities of the alkaloid if administered by hypodermic injection.

* For a vivid description of the physiological effects of morphine read De Quincey, Confessions of an Opium-eater.

CINCHONINE AND QUININE

According to a South American tradition dating back to 1638, the Countess of Cinchon, vice-queen of Peru, recovered from a fever after drinking an extract from the bark of a tree. The generic name, *Cinchona,* was later applied to the trees yielding similar products, and the first alkaloid isolated from the bark was called cinchonine.

Cinchonine, $C_{19}H_{22}N_2O$, crystallizes in prisms melting at 255°. It is a strong bi-tertiary base, dextro-rotatory, almost insoluble in water, soluble in alcohol, and much like quinine in its chemical and physiological reactions. Quinine is a methoxy derivative of cinchonine. The two alkaloids occur together and they are usually associated with traces of at least twenty other related bases.

Quinine is the most important member of the group. On account of its remarkable antipyretic action quinine is a drug of great therapeutic value. It is not a poison in the ordinary sense of the term, still it is far from harmless if taken in large doses. It retards all vital processes, inhibiting every type of metabolic change.

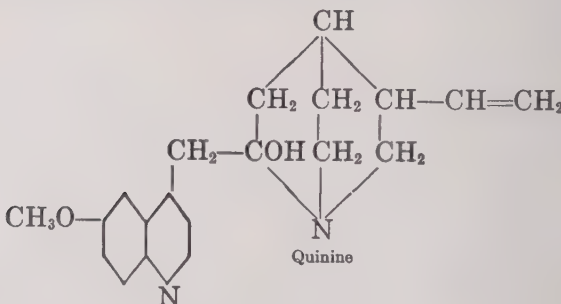
Quinine is used quite generally to combat fevers. Its efficacy, however, depends to some extent upon the nature and origin of the disorder. Its germicidal action on the malarial organism is specific, and it probably plays a similar rôle in the treatment of typhoid fever.

Quinine and cinchonine are converted into toxic isomers through the agency of acetic or citric acids. The change consists of the migration of a hydrogen atom from carbon to nitrogen, converting an enol into a keto structure (see formula on following page).

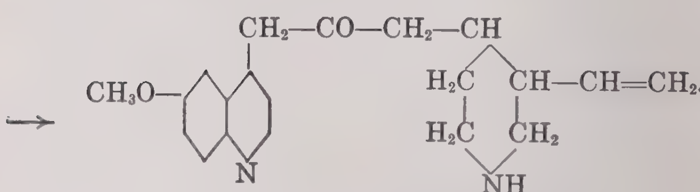
Biddle * discovered that the rate of change of quinine into quinotoxine, or cinchonine into cinchotoxine, is proportional to the concentration of undissociated acid present, the rearrangement being inhibited by hydrogen ions. Hydrogen ions, furnished by the hydrochloric acid of the gastric juice, prevent the conversion of quinine into its poisonous isomer. Sodium acetate, administered with quinine, suppresses the ionization of the hydrochloric acid in the stomach and promotes the rearrangement. Sallmann † denies that there is any danger in

* Biddle, *J. Am. Chem. Soc.*, **38**, 90 (1916).
† Sallmann, *J. Am. Med. Assoc.*, **76**, 999 (1921).

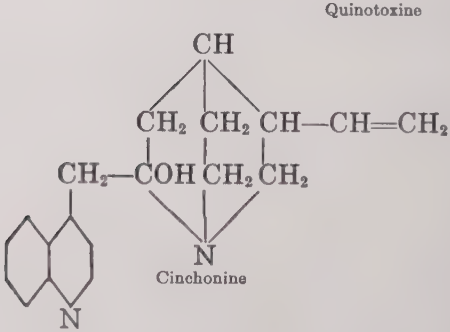
the use of quinine with an organic acid, for he maintains (1) that the conversion proceeds so slowly that only traces of quinotoxine could be formed during the few hours the drug remains in the stomach, (2) that the conversion cannot occur in the alkaline medium of intestinal fluids, and (3) that quinotoxine is not as poisonous as it is commonly believed to be.



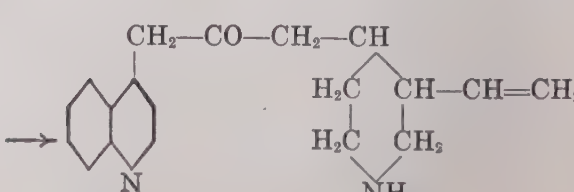
Quinine



Quinotoxine



Cinchonine



Cinchotoxine

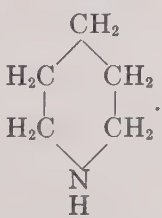
PIPERINE

A crystalline alkaloid known as piperine, $C_{17}H_{19}NO_3$, is found in the berries of the pepper tree. It is almost insoluble in water, but dissolves in alcohol or ether. It melts at 128°–129° and is optically inactive. It is a very weak base, neutral to litmus, and insoluble in dilute acids. It forms salts with concentrated hydrochloric, sulphuric, and nitric acids, but these addition products are rapidly and almost completely hydrolyzed when dissolved in water, the free base being precipitated.

Piperine is hydrolyzed by an alcoholic solution of potassium hydroxide, the products being piperidine and piperic acid:

$$\underset{\text{Piperine}}{C_{17}H_{19}NO_3} + H_2O \longrightarrow \underset{\text{Piperidine}}{C_5H_{11}N} + \underset{\text{Piperic acid}}{C_{12}H_{10}O_4}.$$

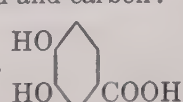
The constitution of piperidine is known (p. 342). It is formed from cadaverine (pentamethylene-diamine) by loss of ammonia, and is easily oxidized to pyridine. Its structural formula is



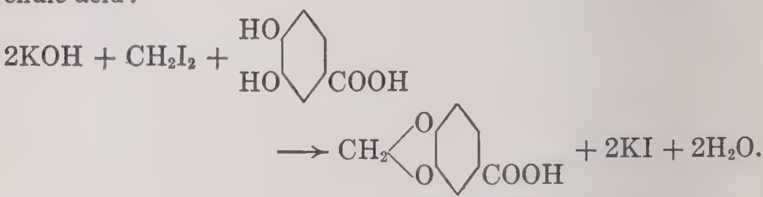
Piperic acid, $C_{12}H_{10}O_4$ (m.p. 217°), is an unsaturated monobasic acid. It is only slightly soluble in water, but dissolves readily in carbon disulphide, and can be titrated with a standard solution of bromine in carbon disulphide. It absorbs four bromine atoms per mol of acid. The unsaturation, therefore, corresponds to the presence of two double bonds. Potassium permanganate oxidizes piperic acid to an aldehyde, piperonal, and finally to the corresponding acid, piperonylic acid:

$$\underset{\text{Piperic acid}}{C_{12}H_{10}O_4} \longrightarrow \underset{\text{Piperonal}}{C_8H_6O_3} \longrightarrow \underset{\text{Piperonylic acid}}{C_8H_6O_4}.$$

Piperonylic acid (m.p. 228°) is decomposed by hydrogen iodide at 180°, or by water vapor at 225°, with the formation of 3, 4-dihydroxybenzoic acid and carbon:

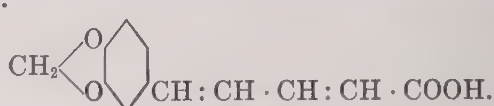
$C_8H_6O_4 \longrightarrow$  $+ C.$

It is regenerated from 3, 4-dihydroxybenzoic acid (protocatechuic acid) by treatment with methylene iodide and an alkali. Piperonylic acid is, therefore, the methylene ether of protocatechuic acid:



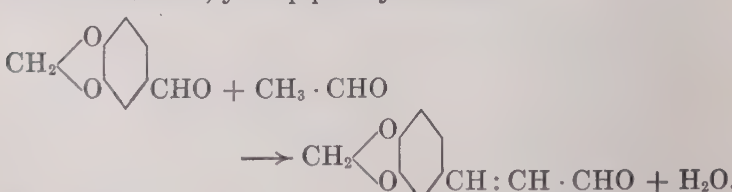
Piperonylic acid

Piperic acid differs from piperonylic by C_4H_4, and since the latter has only one carboxyl group attached to the ring, and is derived from piperic acid by oxidation, the C_4H_4 and the carboxyl group belong to the same side chain. Moreover, the side chain must be unsaturated to account for the absorption of four bromine atoms. The following structure meets these demands:

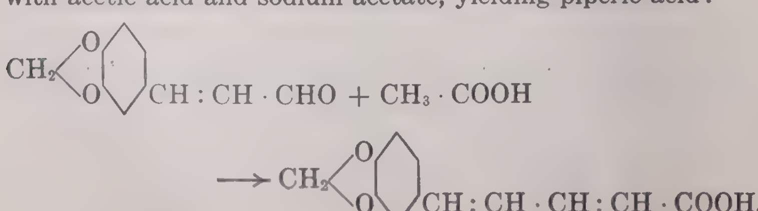


Piperic acid

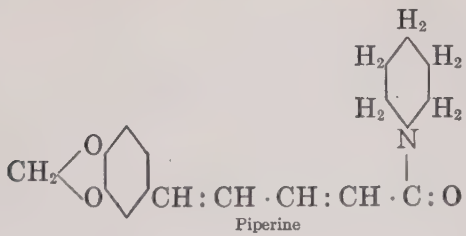
This structure has been confirmed by a synthesis of the acid. Piperonal and acetaldehyde, when dissolved in very dilute alkali and warmed, yield piperonylacrolein:



This aldehyde condenses in a similar way (Perkin's synthesis) with acetic acid and sodium acetate, yielding piperic acid:



Piperine is a condensation product of piperic acid and piperidine. On hydrolysis it yields these compounds. Hence its formula is



Piperine

ESSENTIAL OILS

Volatile oils, characterized by agreeable odors or flavors, may be extracted from the leaves and bark of many trees and from flowers. Such extracts have been used as flavors and perfumes since the dawn of history. They are known as essences or essential oils.

Incense has been used in certain forms of religious worship for many centuries, fragrant roots, stems, or leaves being burned to release the volatile and aromatic constituents. In the earliest writings of the Chinese, the Greeks, and the Egyptians, reference is made to the use of herbs for the preparation of perfumes. Fragrant ointments (balms) were employed by the early Egyptians for the treatment of wounds and for preserving dead bodies (embalming).

Many of the volatile extracts from plants consist chiefly of hydrocarbons having the formulas C_5H_8, $C_{10}H_{16}$, and $C_{15}H_{24}$, called hemi-terpenes, terpenes, and sesqui-terpenes, respectively; or of compounds derived from these hydrocarbons by oxidation. Even in essential oils that are composed primarily of hydrocarbons the characteristic odors and flavors are due to the presence of oxygen compounds including phenols, alcohols, esters, aldehydes, and ketones. In comparatively few cases do we find the origin of these properties in hydrocarbons. Many of the flavors and perfumes on the market to-day are synthetic products. In most instances the artificial preparation contains the identical chemical compound that imparts the desired scent or taste to the natural extract. In other cases these properties are merely imitated by substitution of other types of compounds having flavors or odors similar to those of the natural products. It must be remembered, however, that the extract from a leaf or a flower contains a large number of aromatic bodies, whereas the corresponding synthetic product contains, as a rule, only the one chemical substance that has been found to yield what we recognize as the

characteristic odor or taste of the natural extract. On that account the two preparations are not identical.

TERPENES

A dozen or more liquid hydrocarbons and at least two crystalline compounds corresponding to the formula $C_{10}H_{16}$ constitute the group known as terpenes. Most of them occur in nature, but a few members of the group are synthetic products of the laboratory only. They fall into three general classes: (1) open chain or olefinic terpenes, (2) mono-cyclic terpenes, and (3) bi-cyclic terpenes. The first group consists of unsaturated open chain polymers of isoprene that are more or less readily converted into cyclic derivatives. Members of the second group contain one closed ring, and either in the ring, or in side chains, or distributed between the two, they have two double bonds. The bi-cyclic or bridged-ring terpenes have only one double bond. The second and third classes may be regarded as derivatives of methyl-isopropylbenzene (cymene) or of menthane which is hexahydrocymene.

OLEFINIC TERPENES AND THEIR DERIVATIVES

Citronellal. As a representative of the group we may consider first citronellal, $C_{10}H_{18}O$, a derivative of the unsaturated hydrocarbon 2,6-dimethyl-octadiene-1,7. It occurs in Eucalyptus oil and in the oils of citrus fruits. It is a colorless liquid, boiling at 105° (25 mm.). Citronellal is an aldehyde, for it reacts with hydroxylamine and other reagents that attack the carbonyl group; and it yields an acid with ten carbon atoms, if treated with a mild oxidizing agent. It is readily reduced to an alcohol. Vigorous oxidation breaks it into acetone and β-methyladipic acid, $(CH_3)_2CO$ and $COOH\cdot CH_2\cdot CH_2\cdot CH(CH_3)\cdot CH_2\cdot COOH$ or into methyl alcohol and the keto-aldehyde,

$$CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH(CH_3)\cdot CH_2\cdot CHO.$$

All of these reactions are readily accounted for on the assumption that citronellal has the formula:

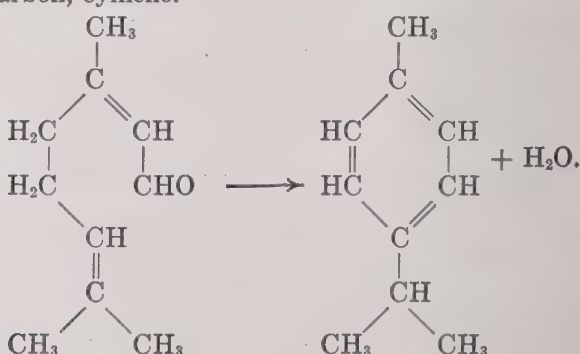
$$\begin{array}{l} CH_3\diagdown \\ \qquad\quad C\cdot CH_2\cdot CH_2\cdot CH_2\cdot \overset{\overset{CH_3}{|}}{CH}\cdot CH_2\cdot CHO \\ CH_2{/\!\!/} \end{array}$$

Citral. Closely related to citronellal is another aldehyde, citral or geranial, $C_{10}H_{16}O$, representing a higher state of unsaturation. It has the formula

$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>C:CH\cdot CH_2\cdot CH_2\cdot \overset{\displaystyle CH_3}{\overset{|}{C}}:CH\cdot CHO.$$

Citral

Citral occurs in the oil expressed from lemon and orange peel. It is a mobile, colorless liquid (b.p. 228°), having a strong lemon odor. Lemon oil contains less than 10 per cent of citral, but lemon-grass oil is rich in this substance (60 to 80 per cent), and is the chief commercial source of the compound. It is dehydrated slowly by simply shaking it with dilute sulphuric acid and potassium bisulphate. The product formed is the cyclic hydrocarbon, cymene.



Citral Cymene

Geraniol and linalol. Geraniol, occurring in geranium oil, and linalol, found in oil of lavender, bergamot, and elsewhere, are related to citral, as indicated by the formulas,

$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>C:CH\cdot CH_2\cdot CH_2\cdot \underset{\underset{\displaystyle CH_3}{|}}{C}:CH\cdot CH_2OH,$$

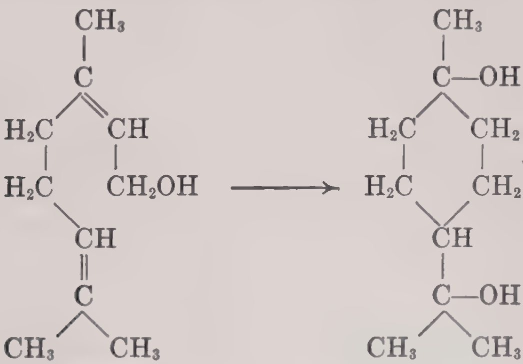
Geraniol (b.p. 122°, 17 m.m.)

$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!\!>C:CH\cdot CH_2\cdot CH_2\cdot \underset{\underset{\displaystyle CH_3}{|}}{COH}\cdot CH:CH_2$$

Linalol (b.p. 198°)

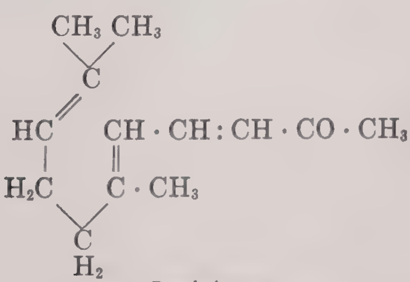
Geraniol may be converted into citral by oxidation with chromic acid or into linalol by the action of steam at 200°.

Geraniol and linalol, when shaken with five per cent sulphuric acid, are converted into terpin by addition of water.



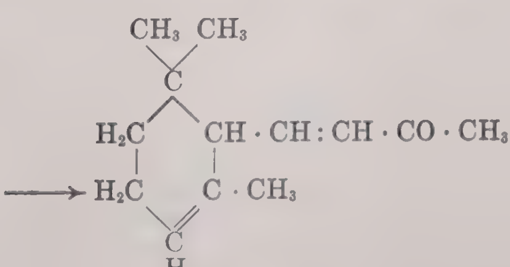
Geraniol Terpin

Ionone and irone. Geranial forms a condensation product with acetone, water being eliminated in the reaction. The substance formed is pseudo-ionone:



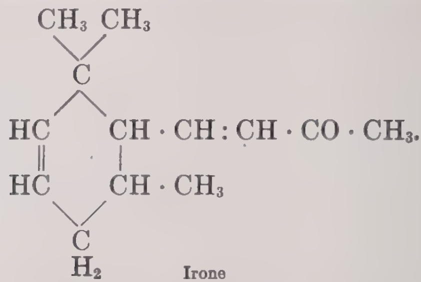
Pseudo-ionone

Warm, dilute sulphuric acid converts pseudo-ionone into ionone:



Ionone

Ionone has the odor of violets and is manufactured for use in perfumes. It differs from irone, the natural violet product, only in the position of a double bond in the ring:

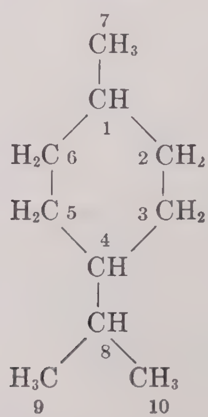


Irone

Both are colorless liquids, very slightly soluble in water but soluble in alcohol and in ether.

MONO-CYCLIC TERPENES

The mono-cyclic terpenes may be regarded as derivatives of the saturated hydrocarbon menthane or hexahydrocymene. As a basis for a systematic nomenclature the carbon atoms of menthane are numbered as follows:

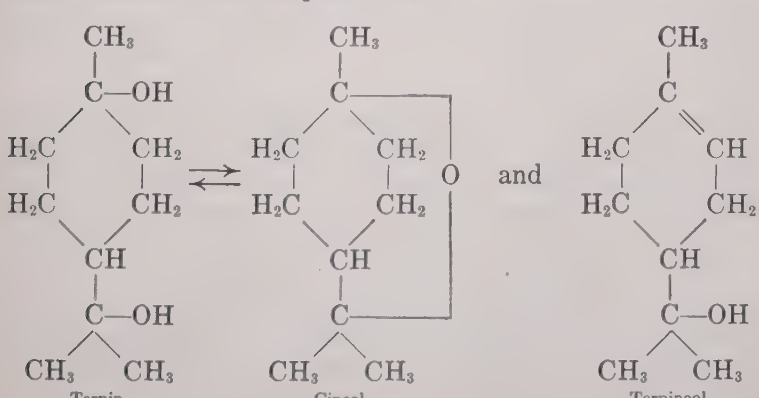


A derivative of this compound with one double bond is a menthene, with two double bonds a menthadiene, etc. The position of a double bond is indicated by the symbol Δ with an index number referring to the first carbon atom involved in the double linkage. If, in order to avoid ambiguity, both of the doubly linked carbon atoms must be specified, the number

corresponding to the second carbon is written within parentheses. Thus the name Δ 2, 4 (8), 5, menthatriene indicates that the compound is a menthane derivative with double bonds between carbon atoms 2 and 3, 4 and 8, 5 and 6. Carbon atom 8 must be specified since number 4 may be doubly bound to either 5 or 8.

The most abundant of all essential oils is turpentine, obtained from the sap of pine trees. It is a mixture of several terpenes and resins. Ordinary rosin is a solid residue obtained by distilling turpentine. Turpentine boils between 155° and 160° and has a specific gravity of about 0.86. Since it is not a pure compound, these properties vary with the source of the oil. It is insoluble in water, but dissolves in alcohol, benzene, or ether. It is a good solvent for phosphorus, sulphur, iodine, rubber, and the resins used in the manufacture of paints and varnishes. The chief constituent of turpentine is pinene, a bi-cyclic compound to be described later. Dipentene, a mixture of *d*- and *l*-limonene, and some other mono-cyclic terpenes are also present. On exposure to air turpentine is slowly oxidized and resinified. Terpin, $C_{10}H_{20}O_2$, an oxidation product of turpentine, is prepared by dissolving turpentine in alcohol and allowing the solution to stand in contact with cold dilute nitric acid for about a week. Water is taken up by the turpentine and crystals of terpin hydrate (m.p. 117°) are formed. Anhydrous terpin melts at 104° and boils at 258°. Its synthesis from geraniol has been mentioned.

Cineol and terpineol are obtained from terpin by shaking the latter with hot dilute sulphuric acid:



Cineol is a liquid (b.p. 177°) with a camphor-like odor; terpineol is a solid (m.p. 35°, b.p. 218°) which crystallizes readily when the mixture is cooled. The reaction indicated above is reversible, terpin being dehydrated by hot dilute sulphuric acid and regenerated slowly from cineol and terpineol in the same solution at low temperatures.

The question as to which of the hydroxyl groups in terpin is removed in the formation of terpineol was settled when it was found that the terpineol formed is a racemic mixture of optically active forms. Carbon atom 4 is asymmetric in the formula given, but asymmetry could not be produced by removing the hydroxyl from carbon atom number 8 with hydrogen from any adjacent carbon atom.

The constitution of terpineol has been established also by direct synthesis. For example, β-iodo-propionic ester reacts with disodio-cyanacetic ester forming γ-cyanopentane-$\alpha\ \gamma\ \epsilon$-tricarboxylic ester:

$$\begin{array}{l} ROOC\cdot CH_2\cdot CH_2I \\ ROOC\cdot CH_2\cdot CH_2I \end{array} + Na_2\overset{\displaystyle CN}{\underset{\displaystyle COOR}{\overset{|}{\underset{|}{C}}}}$$

$$\longrightarrow \begin{array}{l} ROOC\cdot CH_2\cdot CH_2 \\ ROOC\cdot CH_2\cdot CH_2 \end{array}\!\!>C<\!\!\begin{array}{l} CN \\ COOR \end{array} + 2\,NaI.$$

This ester is hydrolyzed by boiling with dilute hydrochloric acid, and when warmed, the free acid loses carbon dioxide.

$$\begin{array}{l} COOH\cdot CH_2\cdot CH_2 \\ COOH\cdot CH_2\cdot CH_2 \end{array}\!\!>C<\!\!\begin{array}{l} COOH \\ COOH \end{array} \longrightarrow \begin{array}{l} COOH\cdot CH_2\cdot CH_2 \\ COOH\cdot CH_2\cdot CH_2 \end{array}\!\!>CH\cdot COOH + CO_2.$$

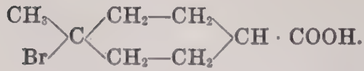
When distilled this product yields water and one more molecule of carbon dioxide and is converted into a closed ring compound, — keto-hexahydrobenzoic acid:

$$CO<\!\!\begin{array}{l} CH_2{-}CH_2 \\ CH_2{-}CH_2 \end{array}\!\!>CH\cdot COOH.$$

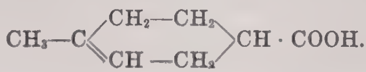
Methyl magnesium iodide reacts with an ester of this acid, the ketone group of the ring being first attacked. The addition product,

$$\begin{array}{r} CH_3 \\ IMgO \end{array}\!\!>C<\!\!\begin{array}{l} CH_2{-}CH_2 \\ CH_2{-}CH_2 \end{array}\!\!>CH\cdot COOR,$$

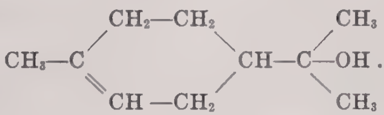
is hydrolyzed and the resulting methyl-hydroxy-hexahydrobenzoic ester is subjected to the action of fuming hydrobromic acid. The hydroxyl group is thus replaced by bromine, the product being



Dilute sodium or potassium hydroxide or even pyridine removes hydrogen bromide from this compound, establishing a double bond in the ring:

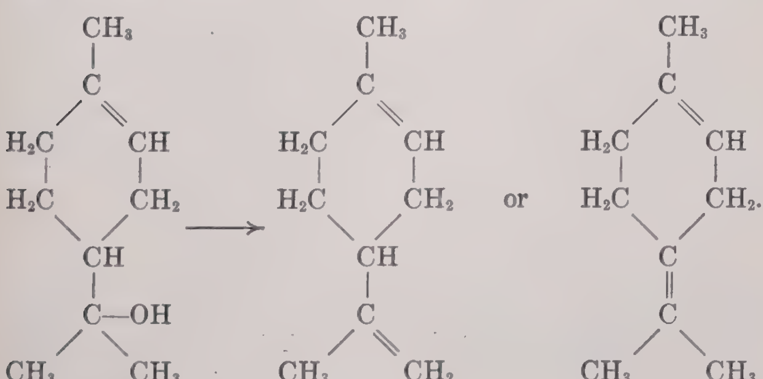


This is esterified once more, treated with an excess of the Grignard reagent (CH_3MgI), and hydrolyzed. The resulting product is terpineol,



Terpineol

Dipentene. Terpineol yields one molecule of water and is converted into dipentene when heated with potassium hydrogen sulphate. There are two possible mechanisms for this dehydration:

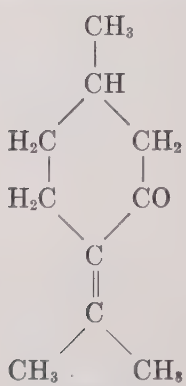


Terpineol I II

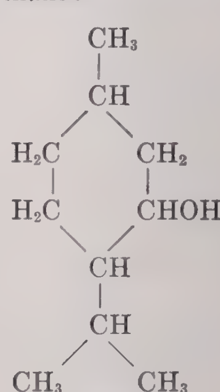
Dipentene is a racemic mixture of optically active hydrocarbons known separately as *d*- and *l*-limonene, and therefore corresponds to formula I in which carbon atom 4 is asymmetric. There is no asymmetric carbon atom in II. Formula II is assigned to another compound, terpinolene, an optically inactive hydrocarbon incapable of resolution into active forms

and obtained from terpineol when the latter is dehydrated by means of a mixture of alcohol and sulphuric acid. Dipentene is a constituent of pine-needle oil, citronella oil, and oil of cubebs. The optically active forms (limonenes) are widely distributed in nature, *d*-limonene being present in lemons, oranges, caraway, dill, and bergamot, and *l*-limonene occurring in spearmint and peppermint. The limonenes are characterized by the formation of crystalline addition products with nitrosyl chloride. The reaction is carried out by adding to the terpene a solution of amyl nitrite in glacial acetic acid. A new asymmetric carbon atom appears as a result of the addition, so that four isomeric derivatives corresponding to the formula $C_{10}H_{16}NOCl$ are formed.

Pulegone and menthol, found in oil of peppermint, are important oxidation products of menthane:



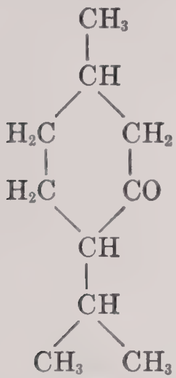
Pulegone



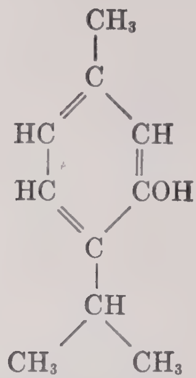
Menthol

Sodium amalgam acts upon an alcoholic solution of pulegone, converting it into menthol. Menthol crystallizes from peppermint oil in slender, colorless needles. It is quite volatile, melts at 43°, and is used therapeutically for some disorders of the nose and throat. The structure assigned to menthol is based upon its conversion into menthane by reduction and into a ketone, menthone, by oxidation. The first process indicates its relationship to cymene, and the second shows that it is a secondary alcohol. The position of the hydroxyl group is determined by forming a dibrom-derivative of menthone and subsequently eliminating two molecules of hydrobromic acid by means of quinoline. Enolization of the compound is

accomplished at the same time. The resulting unsaturated compound is thymol.



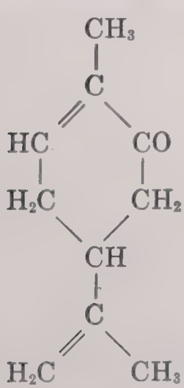
Menthone



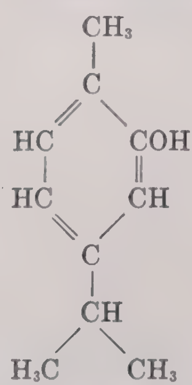
Thymol

When thymol is heated with phosphoric acid, it yields propylene and meta-cresol. The hydroxyl in thymol is thus proved to be meta to the methyl group, and hence the carbonyl group in menthone and secondary alcohol group in menthol must be meta to the methyl radical. Menthone is an intermediate oxidation product between menthol and pulegone. The position of the carbonyl group in the latter is thus established.

The same process of reasoning is used in assigning a definite structure to carvone, a ketone found in oil of caraway, and to carvacrol obtained from carvone by heating with an alkali:



Carvone

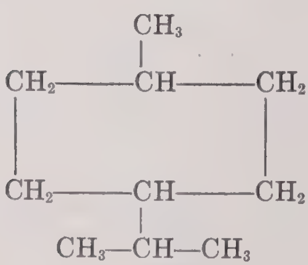


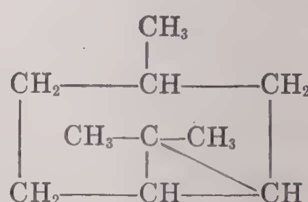
Carvacrol

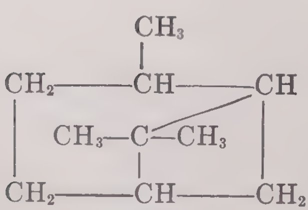
The latter yields propylene and ortho-cresol when warmed with phosphoric acid.

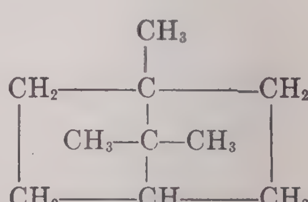
BI-CYCLIC TERPENES

The principal bi-cyclic or bridged-ring terpenes are derivatives of pinene and camphene. Turpentine contains representatives of this series, isomeric with limonene, but capable of forming addition products with only two atoms of bromine or one molecule of hydrobromic acid. That is to say, each molecule in this group has only one double bond, although it has four hydrogen atoms less than the saturated hydrocarbon menthane. They are capable of conversion into terpin, terpineol, or limonene, and, therefore, to account for their degree of unsaturation, they must have two closed chains, that is, two rings. There are three ways of forming a second ring or a "bridged ring" in the menthane molecule, with loss of two hydrogen atoms. Representatives of the three types of compounds are shown in the following structures:

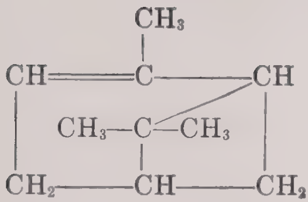

Menthane


Carane

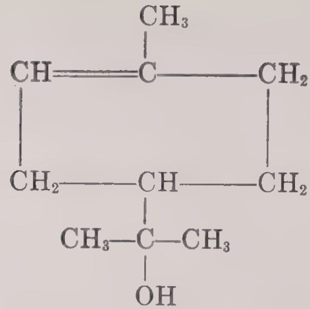

Pinane


Camphane

Pinene, the principal component of turpentine, differs from pinane by two hydrogen atoms. The position of the double bond is determined by the fact that pinene takes up a molecule of water in the presence of acetic acid and benzene-sulphonic acid, breaking the bridge and yielding terpineol:

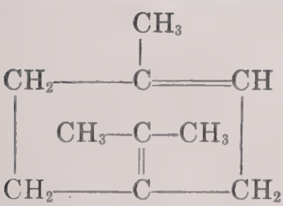


Pinene

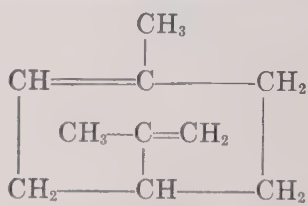


Terpineol

The conversion of pinene into dipentene, which can be accomplished through the agency of an alcoholic solution of sulphuric acid, no doubt involves the formation of terpineol as an intermediate product. Removal of water from terpineol yields either terpinolene or dipentene, depending upon the conditions (p. 371), and in either case the product is isomeric with pinene:



Terpinolene



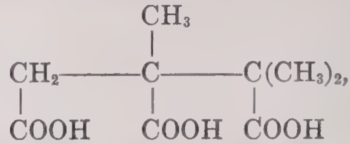
Dipentene

Pinene forms an addition product with hydrogen chloride, the double bond being broken. The compound resembles camphor and is sold as artificial camphor.

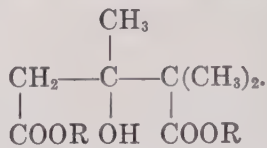
CAMPHOR

The chief component of the essential oil obtained, by steam distillation, from the leaves of the camphor tree is a white, crystalline solid called camphor, $C_{10}H_{16}O$. It sublimes at low temperatures, melts at 175°, and boils at 204°. It is almost insoluble in water but dissolves in organic solvents. It is converted into carvacrol by heating with iodine and into cymene by heating with phosphoric acid. It is obtained from camphene by oxidation with chromic acid. It is a saturated ketone, forming substitution but not addition products. With hydroxylamine it yields a crystalline oxime.

When boiled with nitric acid, camphor yields a dicarboxylic acid, $C_{10}H_{16}O_4$, and finally a tricarboxylic acid, $C_9H_{14}O_6$. The structure of the latter, camphoronic acid, is known to be

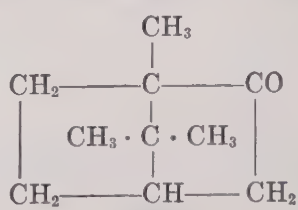


for it has been synthesized as follows: condensation of isobutyric ester and acetoacetic ester yields



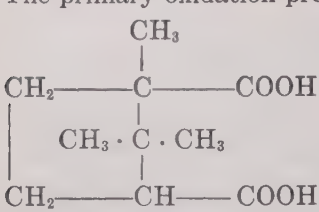
The hydroxyl group is replaced by chlorine through the agency of PCl_3. The chlorine is then replaced by CN through the action of KCN, and the cyanide is converted into the corresponding acid by hydrolysis.

On the basis of this evidence and in harmony with all of its properties, Bredt has assigned to camphor the following formula:



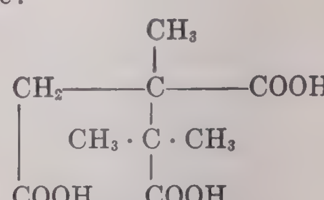
Camphor

The primary oxidation products are:



Camphoric Acid

and

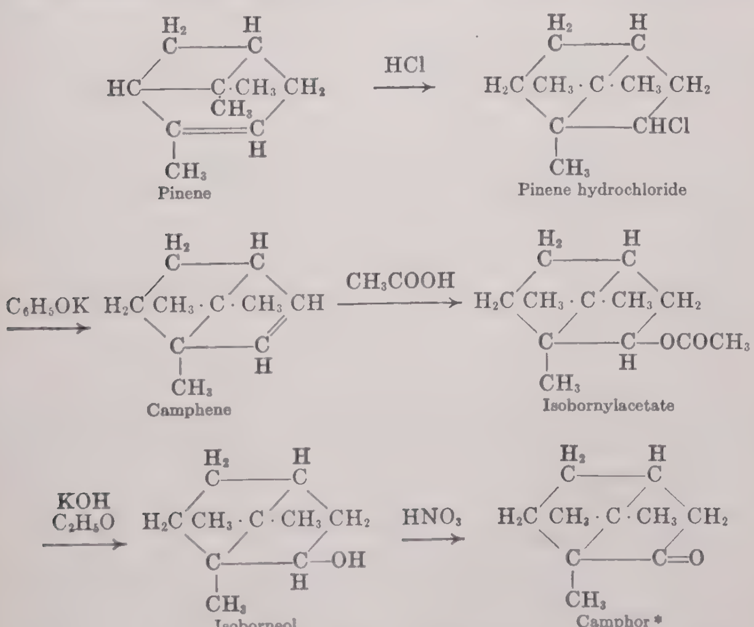


Camphoronic Acid

Camphor may be made from turpentine for about the same price that is now paid for the natural product. The most successful method consists of six steps, as follows: (1) Preparation of fairly pure pinene (b.p. 155°) from crude turpentine by fractional distillation. (2) Conversion of pinene into

pinene hydrochloride by saturating it with dry hydrogen chloride gas at 10° to 15°. The crystalline addition product is obtained by cooling the mixture to −15°, filtering, and recrystallizing from alcohol. It is a soft, snow-white mass of fine crystals (m.p. 118°–120°) having an odor like that of camphor. (3) Preparation of camphene from pinene hydrochloride by digestion with potassium phenolate and subsequent fractional distillation. Camphene distills at 150° to 160°, and therefore is readily separated from the major portion of the phenol (b.p. 180°). Some phenol distills over with the camphene and is washed out by shaking with a solution of sodium hydroxide. The camphene is melted, dried with calcium chloride, and redistilled (m.p. 52°, b.p. 150°). (4) Preparation of isobornylacetate from camphene. This is accomplished by warming camphene with glacial acetic acid and a little sulphuric acid. The product is washed, neutralized with sodium carbonate, and finally distilled in vacuo. It is a liquid, boiling at 102° at 12 m.m. (5) Hydrolysis of isobornylacetate. The ester is heated on a steam bath with an alcoholic solution of potassium hydroxide. Isoborneol separates as a colorless, or slightly yellow, crystalline solid (m.p. 212°). (6) Conversion of isoborneol to camphor. This is done by oxidizing isoborneol with fuming nitric acid at 20°–25°. The reaction mixture is poured upon cracked ice, and camphor separates as a soft, white, crystalline mass. It is purified by steam distillation (m.p. 173°).

The chemistry of these steps is indicated by the following formulas:



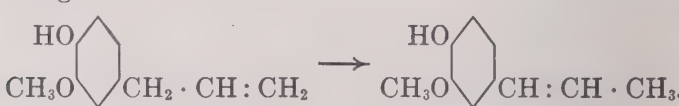
* For proof of structures represented in these reactions and for complete bibliography see Wallach, Terpene und Campher.

FLAVORS AND PERFUMES NOT RELATED TO TERPENES

Wintergreen. Oil of wintergreen is a rare example of an essential oil in which the origin of the flavor and odor can be traced to a single chemical compound. The substance is methyl salicylate. It may be prepared by the action of methyl alcohol on salicylic acid:

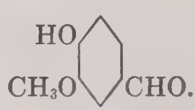
$$C_6H_4\begin{cases}OH\\COOH\end{cases} \xrightarrow{CH_3OH} C_6H_4\begin{cases}OH\\COOCH_3\end{cases} + H_2O.$$

Eugenol and vanillin. The principal component of oil of cloves is eugenol. It is a colorless liquid (b.p. 248°), and is used in the manufacture of some perfumes as well as in flavoring compounds. When boiled with a solution of potassium hydroxide in amyl alcohol, the double bond in the unsaturated side chain shifts its position resulting in the formation of isoeugenol.



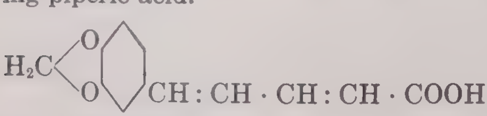
Eugenol Isoeugenol

Isoeugenol is oxidized by potassium permanganate to vanillin. Vanillin is the main component of the flavoring materials in the vanilla bean. It is the methyl ether of protocatechuic aldehyde:

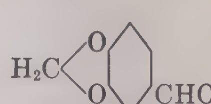


Vanillin

Piperonal (m.p. 37°, b.p. 263°) is a colorless crystalline substance with the odor of heliotrope. It may be made by oxidizing piperic acid.



Piperic acid



Piperonal

The structure of piperic acid was established in connection with the study of piperine (p. 362).

Cinnamic aldehyde. Oil of cinnamon owes its odor and flavor to an unsaturated aldehyde, $C_6H_5 \cdot CH : CH \cdot CHO$, which constitutes from 70 to 80 per cent of the oil. Cinnamic aldehyde boils at 246°, forms a stable addition product with sodium bisulphite, and resinifies when treated with concentrated hydrochloric or sulphuric acid. Cinnamyl alcohol, $C_6H_5 \cdot CH : CH \cdot CH_2OH$, is a crystalline compound, having the oder of hyacinths. It occurs as an ester in many plants, especially in storax.

GENERAL ORGANIC REACTIONS

INTRODUCTION

The study of organic chemistry is simplified by the systematic classification of its multitude of compounds. The hundreds of different chemical substances represent only a few types. We find it necessary to investigate only a sufficient number of individual compounds within a series to learn the changes in properties that generally accompany a definite increment in molecular weight and the changes in properties due to definite alterations of structure. With this foundation an intimate acquaintance with a few of the lower, intermediate, and higher members of the series makes it possible for us to deduce with fair precision the properties of all other known members of the series or to predict the properties of homologues yet undiscovered.

In the same way we may classify reactions. Certain groups may be oxidized, others may be hydrolyzed, diazotized, reduced, or nitrated and so on. We learn to recognize the structures that are susceptible to the actions of various reagents. We learn, also, the conditions that promote the activities of these reagents.

The following pages are devoted to a few very useful general reactions. Except in a few cases, working details are not included. For such details the student must consult laboratory manuals and the chemical hand-books and journals.

HYDROLYSIS

An ordinary double decomposition in which water is one of the reagents is called hydrolysis. Some compounds are hydrolyzed by water alone and at low temperatures, others require the aid of catalysts, or a high temperature, or both. The structures most susceptible to hydrolysis are

$\equiv C—O—C\equiv$, $\equiv C—O—N=$, $=C=N—$, $\equiv C—N=$, $—C\equiv N$, $\equiv C—S—$, and $\equiv C—X$ (X = halogen).

An ether such as $CH_3 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_3$ is not readily hydrolyzed. In the presence of hydrogen ions at high temperatures it reacts with water, slowly forming alcohols. If, however, negative elements or groups be substituted for hydrogen on carbon atoms near the point where cleavage of the molecule occurs, the hydrolysis proceeds readily. The ester $CH_3 \cdot CO \cdot O \cdot CH_2 \cdot CH_3$ may be partially hydrolyzed by water without a catalyst at ordinary temperature. An accumulation of negative groups enhances the tendency to hydrolyze. Thus acetic anhydride,

$$CH_3 \cdot CO \cdot O \cdot CO \cdot CH_3,$$

takes up water more rapidly than does ethyl acetate. The same principle applies to aromatic compounds. Chlorbenzene is not affected by boiling water. Trinitrochlorbenzene is hydrolyzed to picric acid with great ease. In general, the factors influencing the rate of hydrolysis are (1) the structure of the molecule to be hydrolyzed, (2) the catalyst, (3) the temperature, (4) the solvent, and (5) the concentration of the solution with respect to the substance hydrolyzed and to the catalyst. Some of these factors will be considered in connection with typical hydrolytic processes.

Hydrolysis of sugar. Cane sugar presents the first structure listed above, namely, $\equiv C—O—C\equiv$. It is hydrolyzed to dextrose and lævulose under the catalytic influence of hydrogen ions or by the enzyme invertase. The rate of conversion

may be readily followed with the aid of a polariscope, the cleavage being accompanied by a change in optical rotation.

If a represents the weight of sugar present in the original solution, b, its initial rotation, c, its rotation at the end of any interval of time, t, and if d is its final rotation (after the hydrolysis is complete), then the quantity, x, hydrolyzed may be calculated.

$$x = \left(\frac{b-c}{b-d}\right)a.$$

A solution of cane sugar having an optical rotation of 46.75 was hydrolyzed by dilute hydrochloric acid at the rate indicated below.

t(minutes)	d(rotation)	$K = 1/t \log a/a-x$
0	46.75	
15	43.75	.00136
30	41.00	.00133
60	35.75	.00133
90	30.75	.00135
120	26.00	.00137
150	22.00	.00132
210	15.00	.00137
330	2.75	.00146
510	−7.00	.00146
630	−10.00	.00135
Infinite	−18.70	

To find the per cent of the sugar that was hydrolyzed at the end of fifteen minutes we have

$$\left(\frac{46.75 - 43.75}{46.75 - (-18.70)}\right) = \frac{3}{65.45} = 4.58 \text{ per cent.}$$

Influence of hydrogen ion. The rate of hydrolysis of cane sugar varies with the hydrogen ion concentration of the solution. However, it is not a strict proportionality. A half normal solution of nitric acid accomplishes the change six times as fast as does tenth normal nitric acid although the hydrogen ion concentration in the former is less than five times as great as in the tenth normal solution.

Neutral salts. The neutral salt effect has not been explained satisfactorily. A salt of a weak acid usually retards the rate of hydrolysis — a fact that can be accounted for on the basis of its tendency to reduce the hydrogen ion concentration. But it is not obvious that salts like sodium chloride and potassium bromide, when used in connection with hydrochloric or

hydrobromic acid, should accelerate the change. However, this effect has been observed.

Temperature changes. A rise of temperature causes a marked increase in the rate of reaction. The change is too great to be accounted for on the basis of the kinetic theory. In the presence of N/4 HBr cane sugar is hydrolyzed fifty times as fast at 55° as at 25°. It cannot be assumed that an increase of 30° C. accelerates the movements of water and sugar molecules to such an extent that the frequency of collisions between them is increased fifty fold.

Nature of the solvent. Any change in the composition of the solvent affects the rate of chemical action. The addition of alcohol to an acidified aqueous solution of sugar results in a lowering of the rate of hydrolysis. The magnitude of the change in rate is many times greater than would be predicted on the basis of diminished ionization of the acid.

Other reactions show similar effects. Ammonium cyanate is converted into urea thirty times as fast in alcohol as in water. The relative rates of formation of tetraethylammonium iodide from ethyl iodide and triethylamine in various solvents are approximately as follows: hexane 1, ether 4, xylene 10, ethyl acetate 100, allyl alcohol 200, acetone 300, benzyl alcohol, 700. The fact that the reaction proceeds seven hundred times as fast in benzyl alcohol as in hexane cannot be attributed to more frequent collisions of the reacting molecules. It must be due to some specific effect of the solvent that results in an activation of the reagents.

Enzymes. Enzymes usually act selectively. Yeast, for example, contains, or produces, an enzyme which hydrolyzes cane sugar but fails to act upon milk sugar. The specificity of enzyme action is even more strikingly exhibited in connection with the hydrolysis of polypeptides. Trypsin, obtained from the pancreas of living animals through a pancreatic fistula, hydrolyzes alanyl-glycine,

$$NH_2 \cdot CH(CH_3) \cdot CO \cdot NH \cdot CH_2 \cdot COOH,$$

but is without action on glycyl-alanine,

$$NH_2 \cdot CH_2 \cdot CO \cdot NH \cdot CH(CH_3) \cdot COOH.$$

It catalyzes the hydrolytic cleavage of *d*-alanyl-*d*-alanine, but has no effect on *d*-alanyl-*l*-alanine. Racemic polypeptides are

hydrolyzed asymmetrically by enzymes. One isomer usually remains unattacked.

Hydrolysis of an ester. The reaction between water and ethyl acetate may be taken as a typical example of the hydrolysis of an ester:

$$CH_3 \cdot CO \cdot O \cdot C_2H_5 + H_2O \longrightarrow CH_3 \cdot COOH + C_2H_5OH.$$

The reaction is catalyzed by either hydrogen or hydroxide ions. When the reaction is carried out in alkaline solution, the base, as well as the ester, is used up and the reaction is bimolecular:

$$CH_3 \cdot CO \cdot O \cdot C_2H_5 + NaOH \longrightarrow CH_3 \cdot COONa + C_2H_5OH.$$

The velocity of the reaction is proportional to the product of the concentrations of the ester and of the base. If a and b represent the initial molal concentrations of ester and base, respectively, and x is the number of mols of esters hydrolyzed in the time, t, the rate of hydrolysis is indicated by the equation

$$\frac{dx}{dt} = k(a-x)(b-x).$$

In an integrated form

$$k = \frac{1}{t} \cdot \frac{1}{a-b} \cdot \left[\log_e \frac{b(a-x)}{a(b-x)}\right].$$

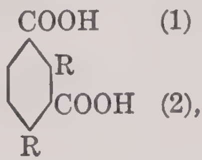
The rate of change may be followed by titrating measured samples of the mixture from time to time. The hydroxide ion concentration diminishes as the reaction proceeds. This type of reaction, involving the disappearance of the base, is called saponification. The term was used first in connection with the technical process of making soaps from fats.

The rate of saponification is proportional to the concentration of hydroxide ions. The value of k, in the equation given above, is constant when strong bases are employed. It is not constant when ammonium hydroxide is used. The ammonium salt formed is highly ionized and the accumulation of ammonium ions reduces the hydroxide ion concentration.

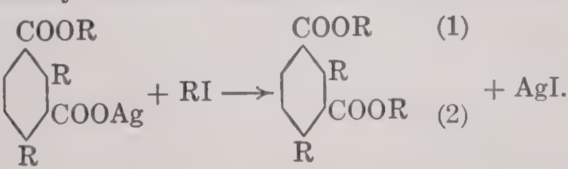
An ester of high molecular weight is hydrolyzed more slowly than one of lower weight whether the difference in mass is due to the alcohol or to the acid in the ester. Thus, the methyl esters of acetic, propionic, butyric, and valeric acids are saponified under identical conditions at rates corresponding approximately

to the numbers 50, 35, 12, and 10. Methyl, ethyl, propyl, and butyl acetates show nearly the same variations in rates.

Structural and stereo-chemical effects on saponification rates have been discussed under steric influences. A single illustration may be given here. In the dibasic acid,



carboxyl group (1) is much more easily esterified than is carboxyl (2). Only one ortho substituent interferes with reactions of the former, whereas the latter, being protected by two ortho side chains, is esterified so slowly by the usual procedure (namely, treatment with an alcohol and hydrogen chloride gas) that this method is not used in actual practice. The second carboxyl group may be esterified, however, by the action of an alkyl iodide on the silver salt of the monoester:



Now, group (1) is much more readily hydrolyzed than is group (2). Hence by this indirect method either one or both of the carboxyl groups may be esterified.

A cyanide or nitrile takes up one molecule of water, forming an amide, or two molecules of water, forming an acid. The first reaction is reversible, an amide, $RCONH_2$, being converted into the cyanide, RCN, and water, by distillation with phosphorus pentoxide.

Amides are readily saponified by boiling with alkalies:

$$R{-}C\begin{matrix}\nearrow O \\ \searrow NH_2\end{matrix} + NaOH \longrightarrow R \cdot C\begin{matrix}\nearrow O \\ \searrow ONa\end{matrix} + NH_3.$$

Sugars and starches are hydrolyzed, in the presence of acids, to monoses, and proteins are converted into peptones, amino acids, and other products, by acids or alkalies, or by the enzymes of the alimentary canal.

Many oximes and hydrazones are converted into the aldehydes or ketones from which they were derived by boiling with hydrochloric acid.

ACETOACETIC ESTER AND MALONIC ESTER REACTIONS

Acetoacetic ester is one of the most useful reagents available for the synthetic processes of organic chemistry. It is, at the same time, an interesting compound from the standpoint of molecular structure. Its configuration was the subject of debate for more than a quarter of a century, and the final solution of the problem established a new type of isomerism, now called tautomerism. The compound corresponds to two structures:

$$CH_3\cdot\overset{\overset{\displaystyle O}{\|}}{C}\cdot CH_2\cdot CO\cdot OC_2H_5 \text{ and } CH_3\cdot\overset{\overset{\displaystyle OH}{|}}{C}:CH\cdot CO\cdot OC_2H_5.$$

The first, or keto structure, represents the compound as a ketone; the second, known as the enol structure, represents it as an unsaturated alcohol. Acetoacetic ester as ordinarily prepared contains molecules of both types in equilibrium with each other. If a reagent which reacts with the enol form only is added to a solution of the ester, the equilibrium is disturbed as the alcohol is removed, and the keto form is progressively changed to the enol by an intramolecular rearrangement, one hydrogen atom shifting its position from carbon to oxygen. The entire quantity, therefore, acts as if it were a pure alcohol. On the other hand, if a reagent is used that removes the keto form, the shift occurs in the opposite direction, and the entire sample behaves as if it were a pure ketone.

The ester is a colorless liquid (b.p. 181°, sp. gr. 1.028) sparingly soluble in water. With ferric chloride it gives a violet-red color due to the presence of a hydroxyl group on a carbon atom which is linked by two bonds to another carbon atom.

The ester is prepared by the condensation of two molecules of ethyl acetate. The mechanism of the process was proved by Claisen.* Ethyl acetate containing a little alcohol is treated with metallic sodium. The sodium alcoholate produced forms an addition product with the ester, and subsequently two

* Claisen, *Ber.*, **20**, 646 (1887).

molecules of alcohol are eliminated by a reaction with a second molecule of the ester:

$$CH_3{-}C\begin{array}{l}\diagup\!\!\!\!\diagup O\\ \diagdown OC_2H_5\end{array} + C_2H_5ONa \longrightarrow CH_3{-}C\begin{array}{l}\diagup ONa\\ {-}OC_2H_5\\ \diagdown OC_2H_5\end{array};$$

$$CH_3{-}C\begin{array}{l}\diagup ONa\\ {-}OC_2H_5\\ \diagdown OC_2H_5\end{array} + CH_3{-}CO{-}OC_2H_5$$

$$\longrightarrow CH_3{-}\overset{\displaystyle ONa \atop |}{C}{=}CH{-}CO{-}OC_2H_5 + 2C_2H_5OH.$$

The sodium may be removed by acidifying this derivative, and acetoacetic ester is liberated in the enol form. It rapidly changes until equilibrium is attained, with approximately 90 per cent in the keto form. Sodium acts upon the ester to regenerate the sodio-derivative in the enol form.

That an addition product of the type indicated above is actually formed is proved by the fact that benzyl benzoate and sodium methylate form an addition product which can be isolated and which is identical with the product formed from methyl benzoate and sodium benzylate:

$$\phi{-}C\begin{array}{l}\diagup\!\!\!\!\diagup O\\ \diagdown OC_7H_7\end{array} + CH_3ONa \longrightarrow \phi{-}C\begin{array}{l}\diagup ONa\\ {-}OCH_3,\\ \diagdown OC_7H_7\end{array}$$

and

$$\phi{-}C\begin{array}{l}\diagup\!\!\!\!\diagup O\\ \diagdown OCH_3\end{array} + C_7H_7ONa \longrightarrow \phi{-}C\begin{array}{l}\diagup ONa\\ {-}OC_7H_7.\\ \diagdown OCH_3\end{array}$$

In regenerating alcohol, through a reaction between the addition product and unchanged ester, hydrogen is removed from the α-carbon atom of the ester. Thus, if ethyl propionate be mixed with the addition product formed from ethyl acetate and sodium ethylate, acetopropionic ester is formed:

$$CH_3{-}C\begin{array}{l}\diagup ONa\\ {-}OC_2H_5\\ \diagdown OC_2H_5\end{array} + CH_3{-}CH_2{-}CO{-}OC_2H_5$$

$$\longrightarrow CH_3{-}\overset{\displaystyle ONa \atop \diagup}{C}{=}\underset{\displaystyle | \atop CH_3}{C}{-}CO{-}OC_2H_5 + 2C_2H_5OH.$$

Sodio-acetopropionic ester

A solution of sodioacetoacetic ester in petroleum ether, cooled to $-60°$ and acidified with anhydrous hydrogen chloride, yields a precipitate of sodium chloride and a solution of the free ester. Evaporation of the solvent at a low temperature leaves the ester in the enol form. It is a liquid that solidifies only when cooled almost to the temperature of liquid air. The keto form crystallizes at $-39°$, and can be obtained nearly pure by freezing it out of the ordinary mixture.

The enol form absorbs bromine rapidly. If the keto form is treated with bromine, the halogen disappears slowly — only as rapidly as the tautomeric change gives rise to enolic molecules. The relative quantities of the two modifications in any mixture may be determined by a measurement of the refractive index of the mixture. The refractive index is always higher for a compound having a double bond between carbon atoms than for an isomeric body with the double bond between carbon and oxygen. If the indices for the two pure forms are known, the composition of a mixture can be calculated from the observed refraction. The velocity of the approach to equilibrium from either side may be determined by measuring the rate of change in the refractive index, by titrating with bromine, or by following the development of color produced by ferric chloride as the quantity of enolic ester increases, or the fading of the color as the keto form increases.

Acetoacetic ester and its homologues may be hydrolyzed in two ways: (*a*) When boiled with dilute sulphuric acid or a dilute aqueous solution of potassium hydroxide, they undergo the ketone decomposition:

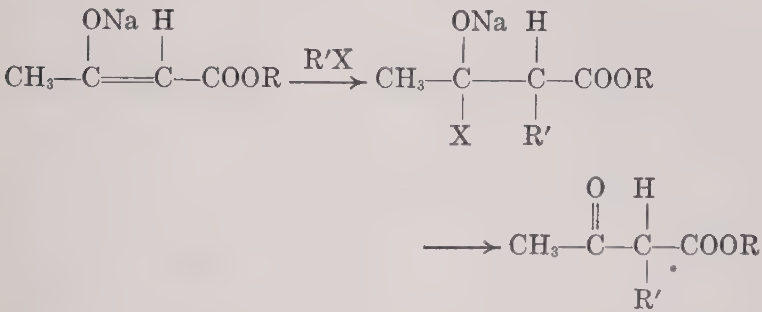
$$\begin{array}{rcccl} CH_3{-}CO{-}\underset{H}{CH_2} & \vdots & {-}COO & \vdots & \underset{OH}{R} \longrightarrow CH_3{-}CO{-}CH_3+CO_2+ROH. \end{array}$$

(*b*) When boiled with a concentrated alcoholic solution of sodium or potassium hydroxide, the acid decomposition is effected:

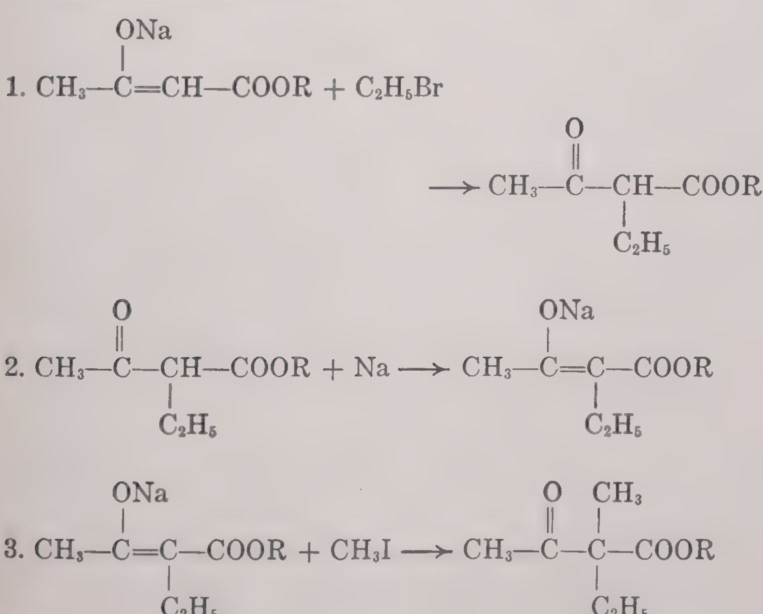
$$\begin{array}{rcccl} CH_3{-}\underset{OH}{CO}{-} & \vdots & \underset{H}{CH_2}CO\underset{H}{O} & \vdots & \underset{OH}{R} \longrightarrow CH_3COOH+CH_3COOH+ROH. \end{array}$$

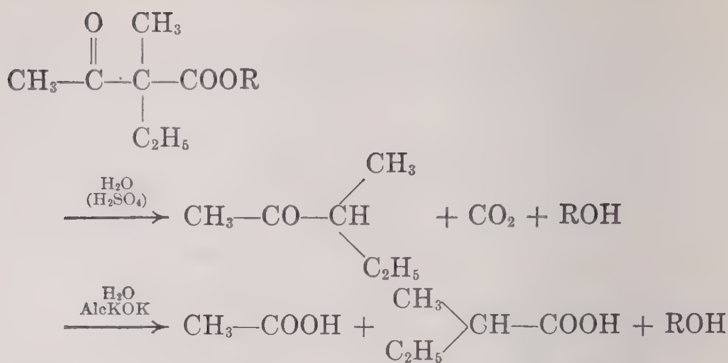
Acetoacetic ester synthesis. Alkyl halides act upon sodioacetoacetic ester, replacing the metal by an alkyl radical. The substituted ester, thus produced has the keto form. The

mechanism of the substitution involves the formation of an intermediate addition product and subsequent elimination of sodium halide.

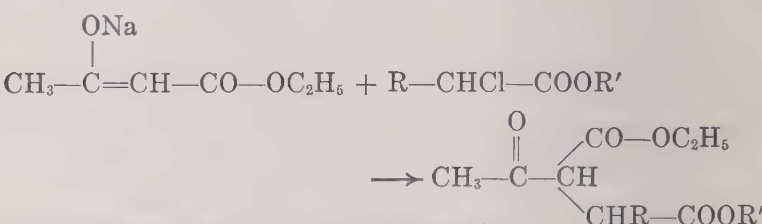


One more hydrogen may be replaced. Sodium acts upon the monoalkyl acetoacetic ester; and the metal, in turn, can be replaced by an alkyl group. By these reactions and subsequent hydrolysis any methyl ketone or any monoalkyl or dialkyl acetic acid may be prepared. The steps involved in a typical procedure are indicated below.



4. 

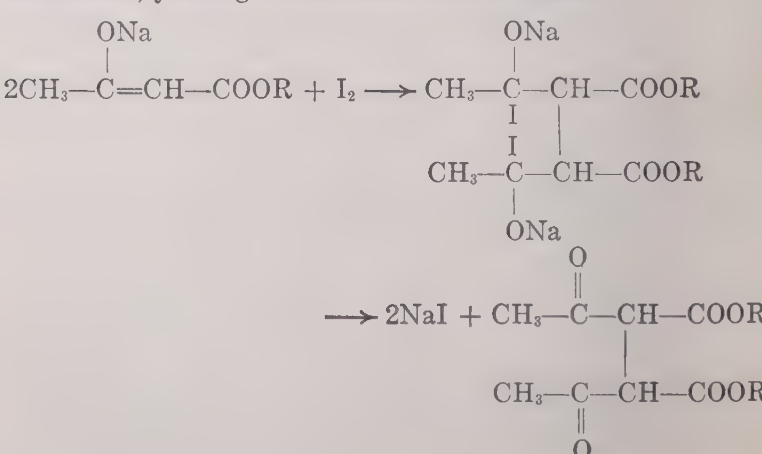
Esters of the α-halogen substituted acids may be used instead of alkyl halides in the reactions outlined above. The ketonic acids are produced in this way:



By the ketone decomposition, this yields

$CH_3—CO—CH_2—CHR—COOH$, CO_2, C_2H_5OH and ROH.

Iodine removes sodium from two molecules of sodio-aceto-acetic ester, yielding a derivative of succinic acid:



When hydrolyzed by boiling with a solution of potassium carbonate, this compound loses carbon dioxide and yields acetonylacetone, $CH_3—CO—CH_2—CH_2—CO—CH_3$.

The entering group does not always attach to carbon when sodium is removed from sodioacetoacetic ester. Some groups take the place vacated by the sodium atom, that is, they form O-derivatives rather than C-derivatives of the ester. In other cases, mixtures of tautomeric forms are produced. The solvent often determines the course of the reaction. An acid chloride, for example, in pyridine solution forms the O-derivative exclusively, whereas the direct action of an acid chloride on sodioacetoacetic ester alone, or in absolute alcohol, gives the C-derivative only:

$$\begin{array}{l} \qquad\quad ONa \\ \qquad\quad\ | \\ CH_3—C{=}CH—COOR + CH_3—COCl \end{array}$$

$$\longrightarrow \begin{array}{c} CH_3—CO—\underset{\underset{\text{(In alcohol)}}{CO—CH_3}}{\underset{|}{CH}}—COOR \end{array} \quad \text{or} \quad \begin{array}{c} CH_3—\underset{\underset{\text{(In pyridine)}}{O—CO—CH_3}}{\underset{|}{C}}{=}CH—COOR \end{array}$$

Malonic Ester

Malonic ester, $CH_2(COOC_2H_5)_2$, is a colorless liquid (b.p. 198°, sp. gr. 1.061 (15°/4°), m.p. – 49.8°). It has an agreeable odor, dissolves readily in alcohol or ether, and is only slightly soluble in water. The aqueous solution is neutral and the free ester is insoluble in alkalies. It, therefore, lacks acidic properties, yet it reacts vigorously with metallic sodium, with an evolution of hydrogen and the formation of a sodium derivative. The sodium derivative is hydrolyzed rapidly by water, with the formation of sodium hydroxide and liberation of the free ester as an insoluble oil.

Malonic ester is prepared from chloracetic acid by neutralizing the acid with potassium carbonate and treating the salt with potassium cyanide. The cyanoacetate thus formed is boiled with alcohol, saturated with hydrogen chloride, and finally poured into ice water. The malonic ester is extracted from the mixture by means of ether in which it readily dissolves.

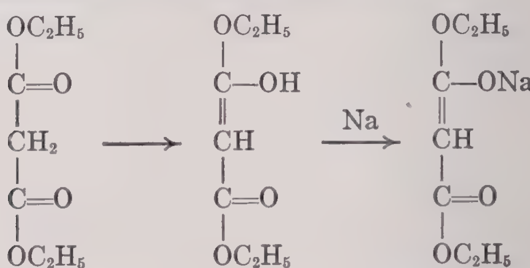
A tautomeric shift, resulting in the formation of an enol structure, is possible here as in the case of acetoacetic ester.

The enol structure for metallic derivatives of acetoacetic ester is fully established; but the evidence of similar structure in malonic ester is not so convincing.

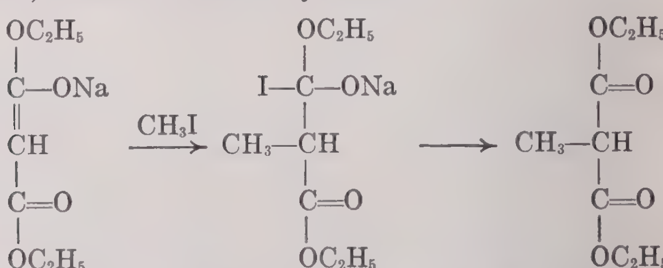
The enol form has never been isolated and the ester fails to give a color with ferric chloride. In all cases when the sodium of sodio-malonic ester is replaced by alkyl or acyl groups, the entering group attaches to the carbon atom. There are no O-derivatives.

A typical malonic ester synthesis is represented in the preparation of propionic acid as follows:

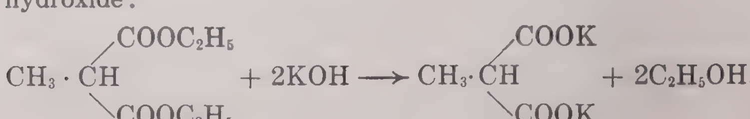
(1) Malonic ester is treated with sodium:



(2) The monosodio-malonic ester, dissolved in absolute alcohol, is warmed with methyl iodide:



(3) The solvent is removed by evaporation and water is added to dissolve the sodium iodide. The diethylmethylmalonate is extracted with ether. After evaporating off the ether the product is purified by fractional distillation, then hydrolyzed by boiling with an alcoholic solution of potassium hydroxide:



(4) The free methyl malonic acid is liberated by warming the salt with the calculated quantity of sulphuric acid:

$$CH_3 \cdot CH\begin{array}{l}\diagup COOK \\ \diagdown COOK\end{array} + H_2SO_4 \longrightarrow CH_3 \cdot CH\begin{array}{l}\diagup COOH \\ \diagdown COOH\end{array}$$

(5) One carboxyl group is eliminated by heating the dicarboxylic acid:

$$CH_3 \cdot CH\begin{array}{l}\diagup COOH \\ \diagdown COOH\end{array} + \text{heat} \longrightarrow \underset{\text{Propionic acid}}{CH_3 \cdot CH_2 \cdot COOH} + CO_2.$$

Any compound having two carboxyl groups attached to the same carbon atom may be decomposed by heating it above its melting point. Carbon dioxide is evolved and one carboxyl group is replaced by hydrogen.

A second alkyl group may be introduced by treating the monoalkyl ester with sodium and an additional mol of an alkyl halide. A dialkyl acetic acid may be made by repeating the process outlined above.

Malonic ester combines with aldehydes and ketones yielding unsaturated acids:

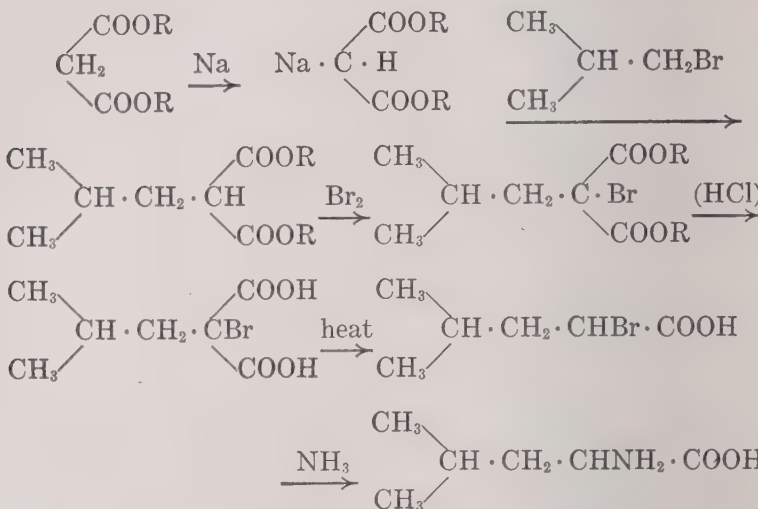
$$R \cdot CHO + H_2C\begin{array}{l}\diagup COOC_2H_5 \\ \diagdown COOC_2H_5\end{array}$$

$$\longrightarrow R \cdot CH : C\begin{array}{l}\diagup COOC_2H_5 \\ \diagdown COOC_2H_5\end{array} + H_2O.$$

After hydrolyzing this product the resulting dibasic acid is heated to expel carbon dioxide. There remains an unsaturated monobasic acid, $R \cdot CH : CH \cdot COOH$.

The methylene hydrogen of malonic ester may be replaced by chlorine or bromine as well as by sodium. The α-halogen and α-amino acids have been synthesized by taking advantage

of this fact. The process may be followed by reference to the following outline:



Leucine

OXIDATION

The oxidation processes most frequently used are designed to accomplish the following transformations.

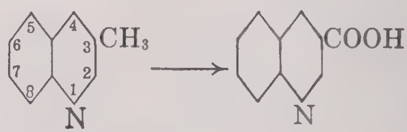
(1) An aliphatic side chain to carboxyl; (2) primary alcohol to aldehyde or acid; (3) secondary alcohol to ketone; (4) phenol to quinone; (5) methylene hydrogen to hydroxyl; (6) oxime to peroxide; (7) hydroxylamine derivative to azoxy compound; (8) hydrazine derivative to azo body.

The principal oxidizing reagents are chromic acid, alkaline and acid solutions of permanganates, nitric acid, hydrogen peroxide, lead dioxide, silver oxide, mercuric oxide, nitrobenzene, bromine, hypobromites, ferric salts, amyl nitrite, and atmospheric oxygen. Many other reagents are used in special cases.

Side chains to carboxyl. An aliphatic side chain on a cyclic nucleus may be oxidized to carboxyl by such reagents as nitric and chromic acids. As a rule the chain is oxidized back to the ring. That is to say, the carboxyl group formed is attached to the ring, regardless of the length of the chain. Thus toluene, ethylbenzene, and propylbenzene all yield benzoic acid on oxidation. This means that the carbon atom attached directly to the ring represents the place that is most susceptible to oxidation. It is a reasonable assumption that oxidation begins there, forming a carboxyl group at once and eliminating the remainder of the chain, which subsequently yields carbon dioxide and water or acids of low molecular weight. In a few instances side chains have been oxidized to alcohol or aldehyde groups; but such cases are exceptional. The temperature and time required for the maximum yield of an oxidation product are factors to be determined experimentally in every new reaction. For details concerning known reactions, we turn to the journals and handbooks. One finds, for example, that *ortho*- and *para*-xylenes are converted into the corresponding toluic acids by dilute nitric acid (1 vol. HNO_3, sp. gr. 1.4, to 3 vols. H_2O), whereas *meta*-xylene requires a concentration of nitric acid twice as

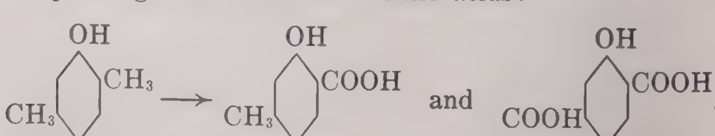
great to yield *m*-toluic acid. Chromic acid converts *meta*- and *para*-xylenes into the corresponding phthalic acids, both methyl groups being converted into carboxyls; but *ortho*-xylene is decomposed by similar treatment. The latter, however, is readily oxidized to *ortho*-phthalic acid by a hot, alkaline solution of potassium permanganate.

The same general rules apply to side chains on heterocyclic rings. The methyl pyridines are converted into picolinic, nicotinic, and isonicotinic acids by hot solutions of potassium permanganate. Alkyl derivatives of quinoline are usually oxidized by heating them on a water bath with dilute sulphuric acid and potassium dichromate. Methyl quinoline is thus converted into quinoline carboxylic acid:



It sometimes requires a long time (two or three days) for complete oxidation of quinoline derivatives. The chromium is precipitated from the reaction mixture by ammonia, and from the filtrate sulphates are removed by barium hydroxide. The excess of barium is later taken out by means of carbon dioxide. The filtrate is then evaporated and the barium salt decomposed by the calculated quantity of sulphuric acid. If there are two or more aliphatic side chains in quinoline, those attached to the benzene nucleus are oxidized first. A group in position 4 is the first attacked on the pyridine side. Position 3 is the next to respond, then 2.

It is often difficult to find suitable conditions for the preparation of oxy-acids from phenols by direct oxidation of a side chain, for the phenols are much more reactive than hydrocarbons and have greater tendencies to break up, yielding compounds of low molecular weight. Fusion with an alkali in the presence of air accomplishes the oxidation in many cases; but the yield is always poor. By this method the cresols have been converted into oxybenzoic acids. The xylenols yield the corresponding monobasic and dibasic acids:



p-Xylenol *m*-Homosalicylic acid Oxyterephthalic acid

Primary Alcohols to Aldehydes and Acids

Oxidation of a primary alcohol results in the formation of an acid, unless the intermediate aldehyde escapes on account of its volatility or is removed by a reaction that is more rapid than the oxidation process. Aniline condenses rapidly with some aldehydes and may be used in such cases to prevent oxidation beyond the aldehyde stage. Esters are often found among the oxidation products of alcohols, due to the formation of acid molecules and their immediate combination with unchanged alcohol.

Ethyl alcohol yields acetaldehyde by the following procedure:

A mixture containing 25 grams of sodium dichromate, 25 grams of alcohol, and 40 grams of water is added in small portions to an equal volume of 50 per cent sulphuric acid. The mixture is boiled 15 or 20 minutes under a reflux condenser, then distilled. A long, well-cooled condenser is used and the receiver is packed in ice. Acetaldehyde boils at 21°. An aqueous solution of the aldehyde is obtained. It is purified by extraction with ether and conversion into the crystalline aldehyde ammonia, from which the pure aldehyde is obtained by distillation with dilute sulphuric acid.

Methyl alcohol is oxidized to formaldehyde by atmospheric oxygen when mixed with air and passed over hot platinum, copper, or nickel. Ethyl alcohol and other members of the same series having fewer than ten carbon atoms are oxidized to aldehydes and acids, without loss of carbon, by air in contact with finely divided metals at temperatures ranging from 150° to 650°. Alcohols of higher molecular weight yield hydrocarbons, carbon dioxide, acids of low molecular weight, and water.

Aromatic alcohols are oxidized by the same methods. In some cases, aromatic halogen compounds (halogen in side chain) may be oxidized to aldehydes by lead nitrate solution. Benzyl chloride, $C_6H_5CH_2Cl$, when boiled with a solution of copper nitrate or lead nitrate, yields benzaldehyde. The process involves replacement of the halogen by hydroxyl and subsequent oxidation of the primary alcohol. Aromatic alcohols, dissolved in chloroform, are oxidized to aldehydes by nitrogen tetraoxide. The reaction is slow, requiring several days, but it is almost quantitative.*

Primary amine to aldehyde. A warm solution of an alkyl amine, in which fine copper powder is suspended, absorbs

* Cohen and Calvert, *J. Chem. Soc.*, **71**, 1050 (1897).

oxygen and acquires a deep blue color. The blue solution, when acidified and distilled, yields an aldehyde.

$$CH_3CH_2NH_2 + O_2 + Cu \longrightarrow CH_3CHO + NH_3 + CuO.$$

Processes involving the use of metals or other contact agents are classified as catalytic methods. Typical examples are (1) the use of hydrogen peroxide and ferrous ions on saturated fatty acids in the synthesis of β-hydroxy and β-ketonic acids, or the conversion of polyhydric alcohols into aldoses by the same reagents; (2) the use of mercury in sulphuric acid to convert amino nitrogen into ammonium sulphate (Kjeldahl method) or to oxidize naphthalene to phthalic acid.

Aldehyde to acid. The aldehyde group is especially susceptible to oxidation, Fehling's solution or silver oxide in ammonium hydroxide being more serviceable than the stronger oxidizing reagents. Many aromatic aldehydes, including benzaldehyde, are converted into the corresponding acids by the oxygen of the air. Fehling's solution (alkaline copper tartrate) fails, however, to oxidize aromatic aldehydes. A method applicable to most of the aromatic aldehydes is that of heating with a saturated solution of potassium hydroxide. Half of the aldehyde molecules are oxidized and half reduced:

$$2C_6H_5CHO + KOH \longrightarrow C_6H_5COOK + C_6H_5CH_2OH.$$

The activity of an oxidizing agent cannot be determined by studying a single reaction. Silver oxide, for example, rapidly oxidizes the aldehyde group —CHO, but fails, in most cases, to break the ethylene linkage —C=C—. On the other hand, potassium permanganate acts faster on the ethylene than on the aldehyde group.

Secondary alcohol to ketone. Chlorine water, chromic acid, and nitric acid are reagents commonly employed to convert secondary alcohols into ketones. Polyhydric secondary alcohols containing no primary alcohol groups are oxidized to ketone-alcohols by solutions of hydrogen peroxide and ferrous sulphate; hydroxy-acids may usually be changed to ketone acids by solutions of potassium permanganate; and diketones are derived from ketone alcohols through the action of nitric acid or an alkaline solution of copper salts. The details of one method may be given.

Dry, powdered benzoin is heated on a water bath with twice its weight of pure concentrated nitric acid for two hours. The mixture is then poured into cold water. Benzil separates as a crystalline, solid mass. It is washed with water until free from acid, then recrystallized from hot alcohol:

$$\underset{\text{Benzoin}}{C_6H_5 \cdot CO \cdot CHOH \cdot C_6H_5} \xrightarrow{HNO_3} \underset{\text{Benzil}}{C_6H_5 \cdot CO \cdot CO \cdot C_6H_5}.$$

Hydrocarbons and phenols to quinones. Most aromatic hydrocarbons resist the action of oxidizing agents. A reagent that acts energetically enough to attack the ring converts it into carbon dioxide and water or other products of low molecular weight. A few of them, however, including anthracene, phenanthrene, and naphthalene, are quite easily converted into the corresponding quinones. Naphthalene is oxidized to phthalic acid by heating it with sulphuric acid in the presence of mercury. Anthracene forms a quinone instead of a nitro-compound when warmed with nitric acid. On a commercial scale, anthraquinone is made by an electrolytic oxidation of anthracene.*

Benzene has been oxidized to quinone by silver peroxide and nitric acid. Silver nitrate reacts with potassium persulphate in nitric acid, forming silver persulphate ($Ag_2S_2O_8$), which, with water, yields silver peroxide, Ag_2O_2, and sulphuric acid. As rapidly as the peroxide is used in the process the remaining silver or silver oxide is reconverted by the acid into the nitrate and by the potassium salt into persulphate. The silver is used repeatedly, and a small quantity suffices to decompose a large amount of the persulphate.

Ortho- and *para*-dihydric phenols are readily oxidized to quinones. Thus hydroquinone is converted into quinone by a solution of a ferric salt or by an alkaline solution of copper sulphate:

$$C_6H_4(OH)_2 + 2Fe^{+++} \longrightarrow C_6H_4O_2 + 2Fe^{++} + 2H^+;$$

$$C_6H_4(OH)_2 + 2Cu^{++} + 2OH^- \longrightarrow C_6H_4O_2 + 2Cu^+ + 2H_2O.$$

Quinones and other types of oxides are formed by the catalytic decomposition of the silver salts of some halogenated phenols. Ethyl iodide and iodine serve as catalysts in these reactions,

* A lead anode is used in an aqueous solution of sulphuric acid (20 per cent) and vanadic acid (2 per cent). Optimum current density 300 amperes per square meter. Temperature 80°.

bringing about the removal of silver and an *ortho-* or *para-*halogen in the form of silver halide.*

Amines to quinones. Aniline sulphate in dilute sulphuric acid is oxidized by dichromate ions at 0° to 10°. The reaction requires about twenty-four hours for completion. From the mixture quinone may be extracted with ether (yellow crystals, m.p. 116°). Intermediate products are formed. The first is said to be phenylammonium oxide, which spontaneously changes to phenylhydroxylamine. *Para*-aminophenol is derived from the latter by intramolecular rearrangement, and finally quinone is formed through oxidation of the aminophenol:

$$C_6H_5NH_2 \longrightarrow C_6H_5NH_2O \longrightarrow C_6H_5NHOH \longrightarrow HOC_6H_4NH_2$$
$$\longrightarrow O:C_6H_4:O.$$

Unsaturated to saturated compounds. The addition of hydroxyl groups to unsaturated compounds is accomplished by the action of a very dilute alkaline solution of potassium permanganate at low temperatures. If there is only one double bond in the molecule, the hydroxyl groups are taken up by the two carbon atoms so bound; but if there are two or more positions of unsaturation in the molecule, and especially in conjugated systems, hydroxyl groups may enter in 1–4 positions, or the molecule may cleave in the position of one double bond and add hydroxyl groups to the other. Thus when crotonic acid, $CH_3 \cdot CH:CH \cdot COOH$, is dissolved in dilute sodium hydroxide or sodium carbonate solution, cooled to 0°, and mixed with an equivalent quantity of 2 per cent potassium permanganate solution, dihydroxybutyric acid is gradually formed. Allylacetic acid, $CH_2:CH \cdot CH_2 \cdot CH_2 \cdot COOH$, by the same treatment is converted into γ-δ-hydroxyvaleric acid,

$$CH_2OH \cdot CHOH \cdot CH_2 \cdot CH_2 \cdot COOH,$$

and cinnamic acid yields phenylglyceric acid:

$$C_6H_5 \cdot CH:CH \cdot COOH \longrightarrow C_6H_5 \cdot CHOH \cdot CHOH \cdot COOH.$$

On the other hand, cinnamenylacrylic acid,

$$C_6H_5 \cdot CH:CH \cdot CH:CH \cdot COOH,$$

yields benzaldehyde, C_6H_5CHO, and tartaric acid,

$$COOH \cdot CHOH \cdot CHOH \cdot COOH.$$

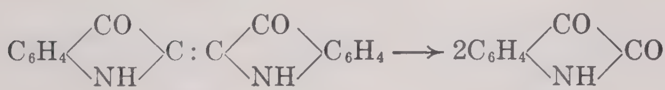
* Hunter and Woollett, *J. Am. Chem. Soc.*, 43, 131, 135 (1921).

Piperic acid, in the same way, yields piperonal and tartaric acid.

Unsaturated acids are oxidized by fusion with sodium hydroxide. Saturated compounds are formed, but as a rule they are not hydroxy acids; the process results in cleavage of the acid between the α- and β-carbon atoms, regardless of the position of the double bond. Oleic acid yields palmitic and acetic acids.

Unsaturated hydrocarbons and alcohols are converted into hydroxy derivatives by shaking with a 1 per cent solution of potassium permanganate. Ethylene yields ethylene glycol, $CH_2OH \cdot CH_2OH$, and allyl alcohol is converted into glycerine.

Cleavage in the position of a double bond with the formation of a ketone group is rather unusual, but an example is afforded in the action of nitric acid on indigo.



Indigo Isatin

Ketones to acids. Chromic acid breaks the ketone molecule with the production of acids. From two to four acids are formed, the number depending upon the structure of the ketone. The cleavage may occur on either side of the carbonyl group. Ethylisobutylketone, $CH_3 \cdot CH_2 \cdot CO \cdot CH_2 \cdot CH(CH_3)_2$, may form acetic and isovaleric acids, or it may split on the opposite side of the carbonyl group and form propionic and isobutyric acids. Usually the cleavage which leaves the ketone carbonyl attached to the shorter chain predominates. However, the principal oxidation products derived from acetonylacetic acid, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOH$, are succinic acid and carbon dioxide. Ethylisopropyl ketone,

$$CH_3 \cdot CH_2 \cdot CO \cdot CH(CH_3)_2,$$

is oxidized to propionic acid and acetone; small quantities of acetic and isobutyric acids are formed also. The acetone formed in the primary reaction is further oxidized and appears ultimately in the form of acetic and carbonic acids.

Saturated as well as unsaturated methyl ketones are oxidized by sodium hypochlorite, the methyl group being removed

as chloroform. Thus benzalacetone yields cinnamic acid and ϵ-ketoheptylic acid forms adipic acid:

$$C_6H_5 \cdot CH:CH \cdot CO \cdot CH_3 + 3NaOCl \longrightarrow C_6H_5 \cdot CH:CH \cdot COONa + CHCl_3 + 2NaOH;$$

$$CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot COOH + 3NaOCl \longrightarrow COONa \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot COONa + CHCl_3 + NaOH + H_2O$$

Amines to alcohols and phenols. Primary aliphatic amines are converted into alcohols by nitrous acid. Phenols are derived from primary aromatic amines in the same way by diazotizing and warming the diazonium salt with water.

Hydrocarbons to alcohols and phenols. A saturated aliphatic hydrocarbon, as a rule, cannot be converted into an alcohol by direct oxidation, for any reagent that oxidizes a hydrocarbon acts even more readily on an alcohol. The usual result of such a reaction is the production of water and carbon dioxide. However, hydrogen held by a tertiary carbon atom is quite easily oxidized to hydroxyl. From triphenylmethane a 90 per cent yield of triphenylcarbinol is obtained by treatment with chromic and acetic acids at the temperature of a water bath. Lead dioxide and sulphuric or hydrochloric acid serve to convert the leucobase of malachite green into the color base:

$$C_6H_5-C\begin{array}{l}\diagup C_6H_4 \cdot N(CH_3)_2 \\ -H \\ \diagdown C_6H_4 \cdot N(CH_3)_2\end{array} \xrightarrow{PbO_2} C_6H_5-C\begin{array}{l}\diagup C_6H_4 \cdot N(CH_3)_2 \\ -OH \\ \diagdown C_6H_4 \cdot N(CH_3)_2\end{array}.$$

In many other types of compounds tertiary carbon displays the same susceptibility to oxidation. Thus, an alkaline solution of potassium permanganate acts upon isobutyric acid, producing oxyisobutyric acid:

$$(CH_3)_2CH \cdot COOH \longrightarrow (CH_3)_2COH \cdot COOH.$$

In a few cases, hydroxyl groups are introduced into aromatic compounds by fusion with sodium or potassium hydroxide. For instance, *meta*-iodophenol, *para*-chlorbenzenesulphonic acid and *ortho*-bromphenol yield resorcin. The hydroxyl group does not always take the position of the replaced group and the number of hydroxyl groups introduced when an aromatic compound is fused with sodium hydroxide, does not always correspond to the number of negative substituents originally in

the ring. Anthraquinone-monosulphonic acid, for example, is oxidized to alizarine (p. 332).

Hydroxylamine to nitroso-compound. Ferric chloride, mercuric oxide, and potassium ferricyanide are suitable reagents for the oxidation of aryl hydroxylamines. Very dilute solutions of permanganates or chromates serve as well. The following method is satisfactory for making nitrosobenzene:

Dissolve 2 grams of phenylhydroxylamine in 100 cc. of 6 per cent H_2SO_4, previously cooled to 0°. Add slowly, with stirring, 150 cc. of an ice-cold 2 per solution of sodium dichromate. Allow the mixture to stand at 0° for an hour, then extract the nitroso-compound with ether.

Oximes to peroxides. An ether solution of benzaldoxime, when saturated with nitrogen trioxide, yields a crystalline precipitate of benzaldoxime-peroxide. In contact with the ether solution of the oxides of nitrogen, it is further oxidized to benzildioxime-peroxide*:

$$\begin{array}{ccccc} C_6H_5 \cdot CH : NOH & & C_6H_5 \cdot CH : NO & & C_6H_5 \cdot C : NO \\ & \longrightarrow & \quad\quad\quad\quad | & \longrightarrow & \quad\;\; | \quad\quad | \\ C_6H_5 \cdot CH : NOH & & C_6H_5 \cdot CH : NO & & C_6H_5 \cdot C : NO \\ \text{Benzaldoxime} & & \text{Benzaldoxime-peroxide} & & \text{Benzildioxime-peroxide} \end{array}$$

* Beckmann, *Ber.*, **22**, 1591 (1899).

REDUCTION

The reducing agents most frequently employed are hydrogen iodide, sodium amalgam, potassium alcoholate, hydrogen, hydrazine, sulphur dioxide, ammonium sulphide, and stannous chloride. In connection with acids or alkalies, iron, zinc, tin, nickel, and other metals are frequently used. Metals are used also as catalysts in reductions with free hydrogen.*

Unsaturated oils are hydrogenated by passing hydrogen gas through the hot oil in which the catalyst is suspended. In this way triolein (from cottonseed oil) is converted into the solid tristearin (the chief component of beef and mutton fats). Rather and Reid applied the same principle in the reduction of unsaturated gases.† Freshly reduced nickel on the surface of fine particles of infusorial earth was suspended in molten paraffin (an inert medium) and a mixture of ethylene and hydrogen was passed through the mixture at 180°. The ethylene was reduced to ethane.

As typical examples of reduction processes we may consider the conversion of acids, aldehydes, and ketones to alcohols; phenols to hydrocarbons; nitro-compounds, cyanides, and azo-compounds to hydrazo-compounds and to amines; and alkyl halides to hydrocarbons.

Aldehydes and ketones to alcohols. Sodium amalgam is a convenient reagent for reductions in aqueous or in alcoholic solutions. The time required for conversion of the carbonyl group to hydroxyl varies from an hour to two or three days, depending not only on the temperature, concentration of the solution, and thoroughness in stirring, but also upon the character of the aldehyde or ketone used.

To a solution of 10 g. of butyric aldehyde in 250 cc. H_2O, 1000 g. of 1% sodium amalgam is added in 100 g. portions. The solution is stirred frequently, and kept slightly acid in reaction as long as hydrogen is being evolved. Butyl alcohol is obtained from the reaction mixture.

* Sabatier and Senderens, Le Catalyse de Chemie.

† Rather and Reid, *J. Am. Chem. Soc.*, **37**, 2115 (1915).

Reduction of a ketone may result in the formation of a ditertiary alcohol or pinacol. Acetone, dissolved in ether, which is saturated with water, is reduced by sodium; or, dissolved in water, it may be reduced by sodium amalgam. In either case two products, namely, isopropyl alcohol and pinacol, are formed:

$$CH_3 \cdot CO \cdot CH_3 + 2H \longrightarrow \underset{\text{Isopropyl alcohol}}{CH_3 \cdot CHOH \cdot CH_3};$$

$$2CH_3 \cdot CO \cdot CH_3 + 2H \longrightarrow \underset{\text{Pinacol}}{\begin{array}{c} CH_3 \cdot COH \cdot CH_3. \\ | \\ CH_3 \cdot COH \cdot CH_3 \end{array}}$$

Benzophenone is reduced by ethyl alcohol to benzpinacol when the solution is exposed to ultraviolet light.*

Alcohol to hydrocarbon. This reduction is accomplished by heating the alcohol with hydriodic acid or with iodine and red phosphorus. The first step in the process consists in replacement of the hydroxyl group by iodine, and with many alcohols the action stops at that point. In other cases hydrogen iodide is eliminated from the saturated halogen derivative, leaving an unsaturated hydrocarbon. The latter is usually reduced further by the same reagents, yielding a saturated hydrocarbon and iodine.

$$C_4H_9 \cdot CH_2 \cdot CH_2OH \longrightarrow C_4H_9 \cdot CH_2 \cdot CH_2I$$
$$\longrightarrow C_4H_9 \cdot CH : CH_2 \longrightarrow C_4H_9 \cdot CH_2 \cdot CH_3$$

Tertiary alcohols and especially those of the aromatic series are very easily reduced; thus, triphenylcarbinol is converted, almost quantitatively, into triphenylmethane by zinc and warm acetic acid. The reaction is completed within two or three hours.

Acid to alcohol. Some acids are converted into primary alcohols by electrolytic reduction.† However, this reaction is not a general one. Many acids yield hydrocarbons when subjected to electrolysis. Acetic acid, for example, yields ethane.

$$\begin{array}{c} CH_3COOH \\ \\ CH_3COOH \end{array} \longrightarrow \begin{array}{c} CH_3 \\ | \\ CH_3 \end{array} + 2CO_2 + H_2$$

* Porter, Ramsperger, and Steel, *J. Am. Chem. Soc.*, **45**, 1830 (1923).
† Tafel and Friedrichs, *Ber.*, **37**, 3190 (1904).

It is much easier to reduce esters, amides, and acyl halides than to reduce free acids.

Nitriles to amines. The alkyl cyanides or nitriles are only slightly soluble in water but quite soluble in alcohol. The latter is, therefore, used as a solvent, and reduction is accomplished by the addition of metallic sodium. The solution is boiled under a reflux condenser, and after about four times the calculated quantity of sodium has been dissolved the mixture is acidified and the solvent is distilled off in vacuo. The free amine is then released by addition of alkali and obtained by distillation or by extraction with ether.

$$R \cdot CH_2CN + 4H \longrightarrow R \cdot CH_2CH_2 \cdot NH_2.$$

Azo compounds to amines. The azo dyes are reduced quantitatively by titanous chloride.* A standardized solution may be used to titrate an aqueous or alcoholic solution of an azo dye, the disappearance of color indicating the end point. The molecules are broken between the nitrogen atoms of the azo group —N═N—, giving rise to amines. Hydrazo compounds are formed as intermediate products, and when less vigorous reducing agents are used, these products may be isolated:

$$C_6H_5{-}N{=}N{-}C_{10}H_6OH + 4Ti^{+++} + 4H^+$$
$$\longrightarrow C_6H_5NH_2 + H_2NC_{10}H_6OH + 4Ti^{++++}.$$

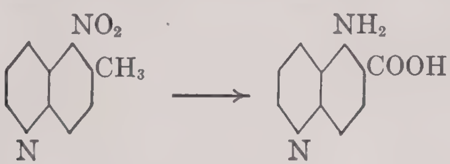
Phenylhydrazones break in the same way when treated with sodium amalgam and dilute acetic acid. The hydrazone is dissolved or suspended in ten to fifteen times its weight of 90 per cent alcohol, then shaken with an excess of 2 per cent sodium amalgam. Acetic acid is added from time to time in sufficient quantities to give the mixture a slightly acid reaction.

Nitro-compounds to amines. Aromatic nitro-compounds may be converted into amines by a great variety of reagents in either acid or alkaline solutions. An exhaustive study of the mechanism of the change and the influence of the environment upon the types of intermediate products formed was made by Haber, who reduced nitrobenzene electrolytically in acid, alkaline, and nearly neutral solutions, and, by varying the current density, was able to produce effects comparable to the results obtainable with weak or strong reducing agents. His results are incorporated in the discussion of nitrobenzene (p. 255).

* Cain and Thorpe, The Synthetic Dyestuffs, p. 336.

In the commercial process of making aniline, iron and hydrochloric acid are used to reduce nitrobenzene. The actual reducing agent is ferrous iron. Very little acid is used. The mechanism of the change involves merely the oxidation of ferrous to ferric iron and simultaneous reduction of nitrobenzene.

Reduction of an aromatic nitro group with simultaneous oxidation of a side chain in the same molecule has been accomplished through the agency of an alcoholic solution of potassium hydroxide. In this way Bogert and Fisher prepared an amino-quinoline carboxylic acid from 5-nitro-6-methyl-quinolin*:



In the same way *ortho*-nitrotoluene is converted into anthranilic acid.

Other reductions. An alkyl halide may be reduced to a hydrocarbon by passing its vapor, mixed with water vapor, over zinc at 150°–170°. Or, if dissolved in alcohol containing water, it may be reduced by boiling with zinc dust. This treatment always results in the formation of mixed products. Thus ethyl iodide yields butane along with ethane. Aromatic halogen compounds behave the same way. Biphenyl, $C_6H_5 \cdot C_6H_5$, is regularly formed in the preparation of phenyl magnesium iodide (Grignard reagent) by the action of magnesium on phenyl iodide, C_6H_5I, in ether.

An alcoholic solution of an alkyl halide, if treated with sodium, usually yields an unsaturated hydrocarbon.

Phenols are reduced by mixing their vapors with hydrogen and passing the mixture over hot nickel. The product is not always a hydrocarbon, however, but is often a ketone or alcohol of the cycloparaffin series. The temperature is the most important factor influencing the course of the reaction.

* Bogert and Fisher, *J. Am. Chem. Soc.*, **34**, 1569 (1912).

ADDITION REACTIONS AND THIELE'S THEORY OF PARTIAL VALENCE

The outstanding characteristic of an unsaturated compound is its capacity to form addition products. In a few cases, both ions or radicals of the added compound are found attached to the same atom in the addition product. This is true in the case of additions to isocyanides, where bivalent carbon is converted into the tetravalent state. In most cases the addition is accomplished by breaking a double bond, an ion or radical of the addendum becoming attached to each of the two atoms originally connected by the multiple linkage. There are many cases, however, in which double bonds are broken, with addition on atoms that are not adjacent. For example, bromine acts upon a compound of the type $R \cdot CH : CH \cdot CH : CH \cdot COOH$ yielding $R \cdot CHBr \cdot CH : CH \cdot CHBr \cdot COOH$. It was stated in an earlier chapter that when polar compounds, such as the halogen acids, are added to unsaturated compounds, the negative ion becomes attached to the carbon atom that is holding fewest hydrogen atoms. Thus hydrogen bromide acts upon propylene, $CH_3 \cdot CH : CH_2$, forming isopropyl bromide, $CH_3 \cdot CHBr \cdot CH_3$. But, contrary to this rule, hydrogen bromide acts upon acrylic acid, $CH_2 : CH \cdot COOH$, forming β-brompropionic acid, $CH_2Br \cdot CH_2 \cdot COOH$.

To account for these anomalies, Thiele advanced a theory of partial valence, which has been quite useful in the classification of addition reactions.

Thiele maintained that although atoms may be joined by double or triple bonds, they do not have twice or three times the affinity for each other as is represented by a single bond, and as a result there is free or unused residual valence on each of the atoms so connected. This partial or residual valence he represented by dotted lines as follows:

$$\begin{matrix} >C & = & C< \\ \vdots & & \vdots \end{matrix} \qquad \begin{matrix} >C & = & O \\ \vdots & & \vdots \end{matrix} \qquad \begin{matrix} -N & = & N- \\ \vdots & & \vdots \end{matrix}$$

According to this view, unsaturated compounds are reactive, because of the free partial valences. Addition takes place on these free residues. The full force of a single bond is then established in the new linkage at the expense of the double bond. Thus the reaction between ethylene and bromine is:

$$\begin{array}{ccccccccccc} CH_2 & : & CH_2 & + Br_2 \longrightarrow & CH_2 & : & CH_2 & \longrightarrow & CH_2 & \cdot & CH_2 \\ \vdots & & \vdots & & \vdots & & \vdots & & | & & | \\ & & & & Br & & Br & & Br & & Br \end{array}$$

Conjugated systems. Compounds having pairs of double bonds separated by single bonds are referred to as conjugated systems. In such cases the partial or residual valences on atoms that are linked together by single bonds may unite and become inactive,

$$\begin{array}{ccccccc} 1 & & 2 & & 3 & & 4 \\ CH_2 & : & CH & \cdot & CH & : & CH_2 \\ \vdots & & \vdots & & \vdots & & \vdots \end{array} \quad \text{becomes} \quad \begin{array}{ccccccc} 1 & & 2 & & 3 & & 4 \\ CH_2 & : & CH & \cdot & CH & \cdot & CH_2. \\ \vdots & & \vdots & \cdots\cdots & \vdots & & \vdots \end{array}$$

Carbon atoms 1 and 4 remain active, but 2 and 3 are mutually satisfied. In compounds of this type 1, 4, addition regularly occurs. The double bond simultaneously shifts to the 2, 3 position. Conjugation is then impossible and the next addition occurs on carbon atoms 2 and 3. Thus the saturation of pentadiene-1, 3 by bromine proceeds in steps as follows:

$$\begin{array}{l} \begin{array}{ccccccccc} CH_3 & \cdot & CH & : & CH & \cdot & CH & : & CH_2 \\ & & \vdots & & \vdots & \cdots\cdots & \vdots & & \vdots \end{array} \xrightarrow{Br_2} \begin{array}{ccccccccc} CH_3 & \cdot & CHBr & \cdot & CH & : & CH & \cdot & CH_2Br \\ & & & & \vdots & & \vdots & & \end{array} \\ \qquad\qquad\qquad \xrightarrow{Br_2} CH_3 \cdot CHBr \cdot CHBr \cdot CHBr \cdot CH_2Br \end{array}$$

α-β-unsaturated acids take up hydrogen bromide in such a way as to produce β-halogen derivatives:

$$CH_3 \cdot CH : CH \cdot COOH + HBr \longrightarrow CH_3 \cdot CHBr \cdot CH_2 \cdot COOH.$$

Thiele's theory affords an explanation. If the bromine had equal chances for combination with the two unsaturated carbon atoms, it would go to the α-position. (Substitution of halogen for hydrogen in saturated acids always gives rise to α-halogen acids.) But the acid presents a conjugated system in which the α-carbon is inactive. The choice presented to the bromine atom is that of combining with the β-carbon or with oxygen.

$$\begin{array}{ccccccc} & & & & & & \diagup OH \\ CH_3 & \cdot & CH & : & CH & \cdot & C{=}O \\ & & \vdots & & \vdots & \cdots\cdots & \vdots \quad \vdots \end{array}$$

Under such circumstances the bromine attaches to the β-carbon, the more positive hydrogen going to the oxygen.

$$CH_3 \cdot CHBr \cdot \underset{\vdots}{C}H : \underset{\vdots}{C}\begin{matrix} \diagup OH \\ \diagdown OH \end{matrix}$$

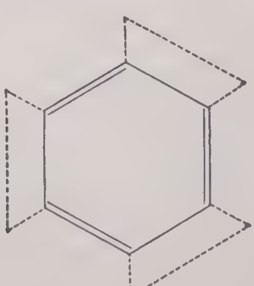
Now, two hydroxyl groups will not, ordinarily, remain attached to the same carbon atom. If the compound were saturated, water would split off, leaving a carbonyl group; but when, as in this case, the carbon to which the hydroxyl groups are attached is doubly linked to another atom, one of the hydroxyl hydrogen atoms migrates to the α-carbon, regenerating the carboxyl group:

$$CH_3 \cdot CHBr \cdot CH : C\begin{matrix} \diagup OH \\ \diagdown OH \end{matrix} \longrightarrow CH_3 \cdot CHBr \cdot CH_2 \cdot COOH.$$

The shift of the position of the double bond when β-γ-unsaturated acids are heated with alkalies was explained by Thiele as due to a tendency to reduce as far as possible the residual valence in such compounds. A conjugated system is more nearly saturated than one having the same number of double bonds in positions that preclude the possibility of conjugation. A shift of the double bond from the β-γ to the α-β position reduces the free partial valences from four to two:

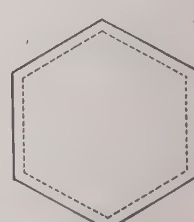
$$\underset{\vdots}{C}H_2 : \underset{\vdots}{C}H \cdot CH_2 \cdot \overset{\diagup OH}{\underset{\vdots}{C}} : \underset{\vdots}{O} \longrightarrow CH_3 \cdot \underset{\vdots}{C}H : CH \cdot \overset{\diagup OH}{C} : \underset{\vdots}{O}$$

Thiele's modification of the Kekulé formula of benzene is written



I

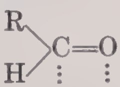
or

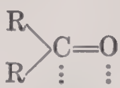


II

Since the molecule is symmetrical and all partial valences are conjugated, there is no reason to suppose that the three ordinary double bonds as written in I are stronger, or that they differ in any respect from the three linkages represented by single bonds and conjugated residual valences. Formula II, therefore, gives an accurate picture of the benzene structure according to the postulates of this theory. Benzene behaves as a saturated compound because it lacks free (unconjugated) residual affinity. It gives no isomeric *ortho*-disubstitution products because the structure is perfectly symmetrical. The assumption of an oscillating double bond was necessary to harmonize the Kekulé formula with the fact that no such isomers exist (p. 232).

The addition reactions of aldehydes and ketones occur in such a way as to satisfy the residual valences of carbon and oxygen in the carbonyl group.


Aldehyde


Ketone

For a discussion of the addition of bromine to ethylene see Stewart and Edlund, *J. Am. Chem. Soc.*, **45**, 1014 (1923).

THE GRIGNARD REACTION

In the year 1901, Grignard* published the results of his experiments on the preparation of alkyl magnesium halides and their applications in synthetic processes. His work led to the development of one of the most important general reactions in the field of organic chemistry.

As early as 1852 Frankland † had reported the preparation of zinc alkyl compounds and had called attention to their remarkable activity. Every year from the time of Frankland's discovery to the beginning of the twentieth century, efforts were made to use the metallic alkides in synthetic work. These attempts were not entirely successful on account of the difficulties encountered in the preparation and use of the reagents.

The Grignard reagent. A weighed quantity of clean, dry magnesium turnings is suspended in pure dry ethyl ether in a flask provided with a reflux condenser. An anhydrous ether solution of an alkyl or aryl halide (containing a quantity of the compound chemically equivalent to the weight of magnesium) is added. A crystal of iodine is sometimes used as a catalyst, but the reaction usually begins at once without a catalyst and becomes violent if not retarded by cooling. Heat is evolved and the ether boils vigorously. If it fails to boil spontaneously, the mixture is warmed on a water bath until the magnesium is dissolved. The reaction between magnesium and the alkyl halide is represented by the equation,

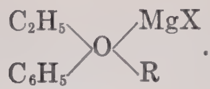
$$RX + Mg \longrightarrow RMgX.$$

The product RMgX is known as the Grignard reagent.

In consideration of the fact that the reagent generally retains one molecule of ether when the solution is evaporated to dryness, many investigators have assumed that it should be considered an oxonium compound of the type,

* Grignard, *Annales de Chem. et de Phys.*, 7th series, **24**, 433 (1901). For a complete bibliography of the Grignard reaction see West and Gilman, Organo-magnesium Compounds, *National Research Council Reprint No. 24* (1922).

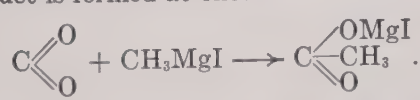
† Frankland, *Phil. Trans.*, **142**, 417 (1852). *Ann.*, **85**, 329 (1853).



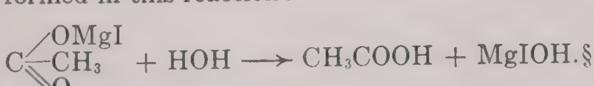
Other support for this conclusion is based upon the fact that magnesium is not attacked by alkyl halides in the presence of such solvents as benzene, toluene, and the paraffin hydrocarbons. The reagent can be prepared, however, in benzene-ether mixtures containing much less ether than the quantity theoretically required to produce the oxonium compound*; or it may be prepared in the absence of any oxygen compound, as, for example, in dimethyl aniline† or in quinoline.‡ It is true that the solvent is held more or less firmly by the organo-magnesium compound, but it is equally certain that the solvent may be removed until the quantity remaining falls far below the limits demanded by the oxonium formula. In fact some alkyl magnesium halides have been prepared by the action of the metal and the alkyl halide in the absence of any other substance.

Side reactions reduce the yields of organo-magnesium compounds. The most important deviation from the main reaction is due to the tendency of magnesium to act upon alkyl halides with the formation of magnesium halide and hydrocarbons. With potassium, sodium, or even with zinc, instead of magnesium, this is the normal course taken (Würtz' synthesis).

Carbon dioxide. When a stream of carbon dioxide is passed into an ether solution of methyl magnesium iodide, a crystalline addition product is formed at once:



The ether solution is poured upon crushed ice to hydrolyze the addition product. Hydrochloric or sulphuric acid is added to prevent precipitation of magnesium hydroxide. Acetic acid is formed in this reaction:



* Tschelinzeff, *Ber.*, **37**, 4534 (1904).

† Tschelinzeff, *Ber.*, **37**, 2081 (1904).

‡ Sachs and Sachs, *Ber.*, **37**, 3089 (1904).

§ In the acid solution the salt, MgIOH, does not exist. The products are MgI_2 and $MgCl_2$, or $MgSO_4$, or the ions of these salts.

Homologues of acetic acid may be prepared in the same way by substituting for the methyl group any other alkyl radical. Benzoic acid and its homologues may be prepared with equal ease by using aryl magnesium halides. The influence of the halogen, though usually slight, cannot be ignored. In this case it is quite an important factor. Magnesium phenyl iodide with carbon dioxide gives a good yield of benzoic acid.* The corresponding bromide yields very little benzoic acid, the principal products being triphenylcarbinol and benzophenone. The three products are formed simultaneously under any circumstances, but either may be made to predominate by suitably modifying the conditions of the experiment:

$$(1)\quad C_6H_5MgBr + CO_2 \longrightarrow C_6H_5C\left\langle\begin{array}{l}OMgBr\\ O\end{array}\right.$$

$$\xrightarrow{H_2O}\ \underset{\text{Benzoic acid}}{C_6H_5COOH} + MgOHBr;$$

$$(2)\quad 2C_6H_5MgBr + CO_2 \longrightarrow \begin{array}{l}C_6H_5\\ C_6H_5\end{array}\!\!\Big\rangle C\Big\langle\!\!\begin{array}{l}OMgBr\\ OMgBr\end{array}$$

$$\xrightarrow{H_2O}\ \underset{\text{Benzophenone}}{\begin{array}{l}C_6H_5\\ C_6H_5\end{array}\!\!\Big\rangle CO} + MgBr_2 + Mg(OH)_2;$$

$$(3)\quad 3C_6H_5MgBr + CO_2 \longrightarrow (C_6H_5)_3COMgBr + MgO + MgBr_2,$$

$$(C_6H_5)_3COMgBr + HOH \longrightarrow \underset{\text{Triphenyl carbinol}}{(C_6H_5)_3COH} + MgBrOH.$$

A quantitative yield of triphenylacetic acid is obtained when triphenylmethyl magnesium chloride is treated with carbon dioxide:

$$(C_6H_5)_3CMgCl + CO_2 \longrightarrow (C_6H_5)_3C{-}C\left\langle\begin{array}{l}O\\ OMgCl\end{array}\right.;$$

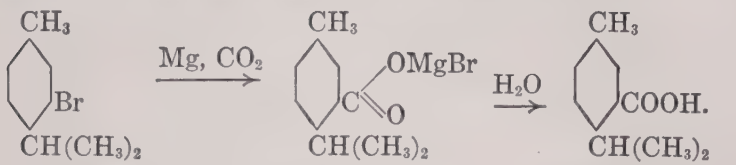
$$(C_6H_5)_3C{-}C\left\langle\begin{array}{l}O\\ OMgCl\end{array}\right. + H_2O \longrightarrow (C_6H_5)_3C\cdot COOH + MgOHCl.$$

The cymene carboxylic acids are made from the corresponding bromides by means of the Grignard reaction.† A few drops of ethyl iodide activates the magnesium so that it dissolves

* Zelinsky, *Ber.*, **35**, 2687 (1902).

† Bogert and Tuttle, *J. Am. Chem. Soc.*, **38**, 1353 (1916).

rapidly in an ether solution of brom-cymene. The ether solution is then cooled to about $-10°$ and kept in contact with carbon dioxide under pressure for eight or ten hours. The product is hydrolyzed with ice and dilute hydrochloric acid:



3-Brom-cymene   Cymene-3-carboxylic acid

Sulphur dioxide,* nitrogen dioxide,† and carbonbisulphide combine with the Grignard reagent, forming compounds analogous to those formed with carbon dioxide.

Water, alcohols, phenols, and amines decompose alkyl and aryl magnesium halides, with the formation of hydrocarbons, as indicated by the following equations:

(1) $2C_2H_5MgBr + 2H_2O \longrightarrow 2C_2H_6 + MgBr_2 + Mg(OH)_2;$

(2) $2C_2H_5MgBr + 2C_2H_5OH \longrightarrow 2C_2H_6 + MgBr_2 + Mg(OC_2H_5)_2;$

(3) $2C_2H_5MgBr + 2C_6H_5OH \longrightarrow 2C_2H_6 + MgBr_2 + Mg(OC_6H_5)_2;$

(4) $C_2H_5MgBr + C_6H_5NH_2 \longrightarrow C_2H_6 + C_6H_5 \cdot N\left\langle\begin{matrix} H \\ MgBr \end{matrix}\right. .$

Amino and hydroxyl hydrogen may be estimated quantitatively by measuring the ethane gas evolved in these reactions.‡

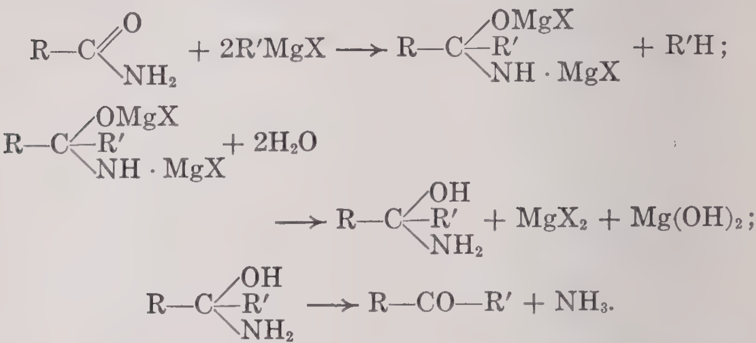
Primary amines are capable of further action. Both amino hydrogen atoms are removed at elevated temperatures (boiling point of the ether solution). A secondary amine, having only one available hydrogen atom, reacts with but one molecule of the reagent. Tertiary amines are inactive. The metallic derivatives formed in these reactions are hydrolyzed rapidly by water, regenerating the original amines, phenols, and alcohols. The carbonyl as well as the amido group in an amide is susceptible to reaction with alkyl magnesium halides. A ketone

* Rosenheim and Singer, *Ber.*, **37**, 2152 (1904). Houben and Kesselkaul, *Ber.*, **35**, 3695 (1902).

† Wieland, *Ber.*, **36**, 2315 (1903).

‡ Hibbert and Sudborough, *Proc. Chem. Soc.*, **19**, 285 (1903).

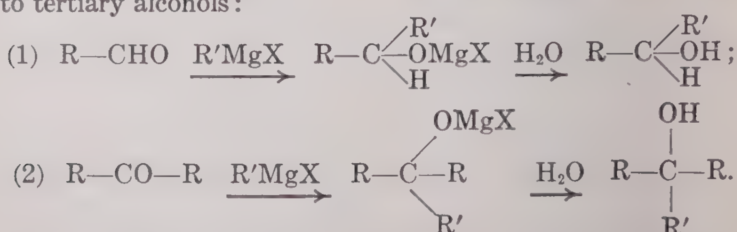
is the final hydrolysis product derived from a primary amide, but the yield is unsatisfactory:



The last step takes place spontaneously at temperatures attained on a water bath.

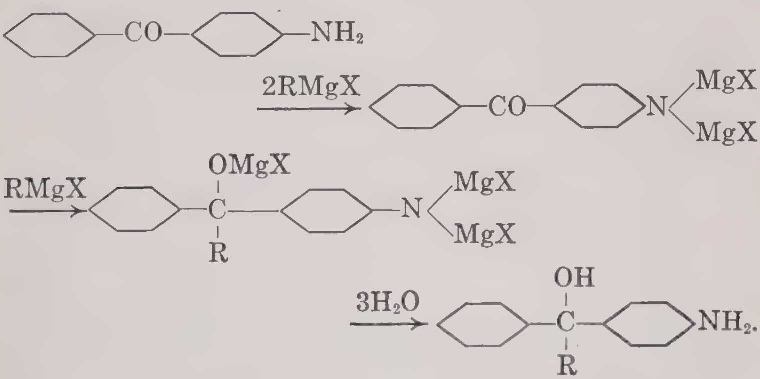
Aldehydes and ketones. The Grignard reagent acts upon aldehydes and ketones, forming compounds which are readily hydrolyzed to alcohols. The details of a typical procedure are stated in the laboratory manual. Generally an ether solution or suspension of the aldehyde is added to an ether solution of the reagent, and the mixture is warmed on a steam bath under a reflux condenser for two or three hours. The reaction mixture is then cooled and slowly poured on cracked ice. The hydrolysis is accompanied by the evolution of heat, and thermal decomposition of the product should be avoided. Enough hydrochloric acid or ammonium chloride is added to the ice to hold the magnesium in solution and the alcohol is extracted with ether.

Formaldehyde gives rise to primary alcohols. All other aldehydes yield secondary alcohols, and ketones are converted into tertiary alcohols:



If the aldehyde or ketone is also a primary or secondary amine, an excess of the reagent must be used, for the speed of

the reaction with an amino group is much greater than with the carbonyl. The latter reacts, therefore, only with the magnesium compound remaining after the amino group has been completely satisfied. With aminobenzophenone, for example, the reactions proceed as follows:*



Acid chlorides and esters. With acid chlorides and esters, the aryl and alkyl magnesium halides form addition products which, upon hydrolysis, yield ketones or tertiary alcohols:

$$\mathrm{R{-}C}\begin{cases}\mathrm{O}\\ \mathrm{OR}\end{cases} \xrightarrow{\mathrm{R'MgX}} \mathrm{R{-}C}\begin{cases}\mathrm{OMgX}\\ \mathrm{R'}\\ \mathrm{OR}\end{cases}$$

$$\xrightarrow{\mathrm{H_2O}} \mathrm{R{-}CO{-}R'} + \mathrm{ROH} + \mathrm{MgXOH}.$$

With an excess of the reagent the alkoxyl group of the ester is replaced by an aryl or alkyl radical.

$$\mathrm{R{-}C}\begin{cases}\mathrm{OMgX}\\ \mathrm{R'}\\ \mathrm{OR}\end{cases} + \mathrm{R'MgX} \longrightarrow \mathrm{R{-}C}\begin{cases}\mathrm{OMgX}\\ \mathrm{R'}\\ \mathrm{R'}\end{cases} + \mathrm{MgXOR};$$

$$\mathrm{R{-}C}\begin{cases}\mathrm{OMgX}\\ \mathrm{R'}\\ \mathrm{R'}\end{cases} + \mathrm{H_2O} \longrightarrow \mathrm{R{-}C}\begin{cases}\mathrm{OH}\\ \mathrm{R'}\\ \mathrm{R'}\end{cases} + \mathrm{MgXOH}.$$

Esters of formic acid yield aldehydes or secondary alcohols. The production of benzaldehyde from ethyl formate and phenyl magnesium bromide is accomplished on a commercial scale. The process was among the first of the patented applications of the Grignard reaction.†

* Porter and Hirst, *J. Am. Chem. Soc.*, **41**, 1261 (1910). † D. R. P. 157573.

Many esters are capable of reacting in more than one way. In cyanacetic ester, for example, the cyanide radical or the carbonyl or both may unite with the reagent. The product formed depends upon the relative velocities of the possible reactions. In this case the fastest action is addition on the —CN group:

$$\begin{array}{l} C\equiv N \\ | \\ CH_2 \\ | \\ C=O \\ | \\ OC_2H_5 \end{array} + RMgX \longrightarrow \begin{array}{l} R \\ | \\ C=N-MgX. \\ | \\ CH_2 \\ | \\ C=O \\ | \\ OC_2H_5 \end{array}$$

On hydrolysis this product yields a ketone ester, which also presents two possibilities for addition of the reagent.

Acetoacetic ester affords similar opportunities for varied activities. Dialkyl acetoacetic ester yields β-hydroxy-acids and ditertiary alcohols:

(1) $CH_3-CO-CR_2-CO-OC_2H_5$

$$\xrightarrow{R'MgX} CH_3-C\begin{array}{l} \diagup OH \\ - \\ \diagdown R \end{array}\!\!-CR_2-CO-OC_2H_5;$$

(2) $CH_3-CO-CR_2-CO-OC_2H_5$

$$\xrightarrow{3R'MgX} CH_3-C\begin{array}{l} \diagup OH \\ - \\ \diagdown R' \end{array}\!\!-CR_2-C\begin{array}{l} \diagup OH \\ -R'. \\ \diagdown R' \end{array}$$

Ditertiary alcohols have been obtained also from diketones. Thus benzil has been converted into diphenyldiethyl glycol:

$$C_6H_5-CO-CO-C_6H_5 \xrightarrow{2C_2H_5MgI} \begin{array}{ccccc} C_6H_5 & OH & & OH & C_6H_5 \\ & \diagdown | & & | \diagup & \\ & C & - & C & \\ & \diagup & & \diagdown & \\ C_2H_5 & & & & C_2H_5 \end{array}$$

Since many tertiary alcohols lose water and form unsaturated hydrocarbons when heated, the Grignard reaction has been used to prepare derivatives of ethylene.

Replacement of Halogens by Alkyl or Aryl Radicals

Chloroform and bromoform react energetically with the Grignard reagent, yielding products in which one or more of the halogen atoms are replaced by hydrocarbon radicals. Triphenylmethane is produced by this reaction:

$$CHBr_3 + 3C_6H_5MgBr \longrightarrow (C_6H_5)_3CH + 3MgBr_2.$$

Benzal chloride yields its chlorine in a similar way, giving the same product:

$$C_6H_5CHCl_2 + 2C_6H_5MgI \longrightarrow (C_6H_5)_3CH + 2MgClI.$$

Carbon tetrachloride yields three of its chlorine atoms in an exchange of this type:

$$CCl_4 + 3\phi MgX \longrightarrow \phi_3CCl + 3MgXCl.$$

Halogens may be replaced by hydrogen, by converting the halide into a magnesium addition product, then decomposing the compound with water. Triphenylchlormethane is thus converted into triphenylmethane:

$$(C_6H_5)_3CCl + Mg \longrightarrow (C_6H_5)_3CMgCl \xrightarrow{H_2O} (C_6H_5)_3CH + MgClOH.$$

Inorganic salts. The halogen salts of mercury, lead, tin, arsenic, antimony, bismuth, silicon, phosphorus, and thallium are decomposed by alkyl and aryl magnesium halides with the formation of organic derivatives of these elements. Phosphorus trichloride, with an excess of phenyl magnesium bromide, yields triphenylphosphine:

$$2PCl_3 + 6C_6H_5MgBr \longrightarrow 2(C_6H_5)_3P + 3MgCl_2 + 3MgBr_2.$$

Mercury biphenyl, tin tetraphenyl, and trimethylarsine are formed with equal ease. The behavior of lead chloride is of interest, a tetra-aryl derivative being produced from the bivalent salt.

$$2PbCl_2 + 4C_6H_5MgBr \longrightarrow Pb + Pb(C_6H_5)_4 + 2MgCl_2 + 2MgBr_2$$

Lead tetraphenyl crystallizes in colorless prisms, melting at 229°.

Unsaturated compounds. Kohler and his co-workers have established very definite laws with reference to the addition of the Grignard reagent to unsaturated compounds presenting

conjugated systems of double bonds.* Aldehydes of the type $R \cdot \overset{4}{C}H : \overset{3}{C}H \cdot \underset{\diagdown H}{\overset{2}{C}} : \overset{1}{O}$ yield 1, 2 addition products. That is, the reagent acts upon the carbonyl group giving

$$R \cdot CH : CH \cdot C \begin{cases} R \\ OMgX. \\ H \end{cases}$$

Ketones follow the same rule if one of the groups attached to the carbonyl is the methyl radical. Other ketones with conjugated systems yield 1, 4 addition products. Thus, from

$$R{-}CH{=}CH{-}C\begin{cases} {=}O \\ C_6H_5 \end{cases} \text{ we obtain } R{-}\underset{\diagdown R}{CH}{-}CH{=}C\begin{cases} OMgX \\ C_6H_5 \end{cases}.$$

On hydrolysis this yields a saturated ketone.

With α-β-unsaturated esters there are three possibilities. The alkoxyl group may be replaced by the radical of the Grignard reagent, or 1, 4 or 1, 2 addition may occur:

$$(1)\quad R{-}CH{=}CH{-}C\begin{cases} {=}O \\ OR \end{cases} + R'MgX \longrightarrow R{-}CH{=}CH{-}C\begin{cases} {=}O \\ R' \end{cases} + MgXOR;$$

$$(2)\quad R{-}CH{=}CH{-}C\begin{cases} {=}O \\ OR \end{cases} + R'MgX \longrightarrow \begin{matrix} R \\ R' \end{matrix}\Big\rangle CH{-}CH{=}C\begin{cases} OMgX \\ OR \end{cases}.$$

$$(3)\quad R{-}CH{=}CH{-}C\begin{cases} {=}O \\ OR \end{cases} + R'MgX \longrightarrow R{-}CH{=}CH{-}C\begin{cases} R' \\ OMgX. \\ OR \end{cases}$$

Reactions (1) and (3) give rise to the same hydrolysis products and we cannot determine which mechanism represents the actual process. If the radical in the Grignard reagent is aromatic, the reaction goes chiefly according to (1) or (3). If the radical is aliphatic, the second equation is favored.

* Kohler and Heritage, *Am. Chem. J.*, **33**, 35 (1905). Kohler and Reimer, *Am. Chem. J.*, **33**, 333 (1905). Kohler, *Am. Chem. J.*, **34**, 132 (1905). *ibid.*, **37**, 369 (1907).

THE FRIEDEL AND CRAFTS REACTION

The catalytic influence of anhydrous aluminum chloride in effecting condensations between aliphatic halogen compounds and derivatives of benzene naphthalene or anthracene was observed by Friedel and Crafts* in 1876. Applications of the reaction have been extended to almost every type of change which involves the elimination of hydrogen chloride, bromide, or iodide. The catalytic action of aluminum chloride is an important aid also in many reactions that do not involve the removal of hydrogen halide, but such uses of the reagent would not be regarded as typical examples of the Friedel and Crafts reaction.

Ferric chloride, ferric bromide, and the corresponding salts of antimony, zinc, and tin may be substituted for the aluminum salt, but, as a rule, aluminum chloride is superior to these and, in many cases, it is the only reagent of practical value in bringing about the condensations.

1. *Side chains introduced.* Homologues of benzene may be made by the action of aluminum chloride on a mixture of benzene and an alkyl halide:

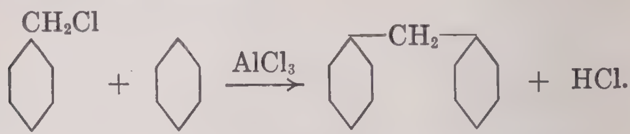
$$C_6H_6 + CH_3Cl \xrightarrow{(AlCl_3)} C_6H_5 \cdot CH_3 + HCl;$$

$$C_6H_5CH_3 + CH_3Cl \xrightarrow{(AlCl_3)} C_6H_4(CH_3)_2 + HCl.$$

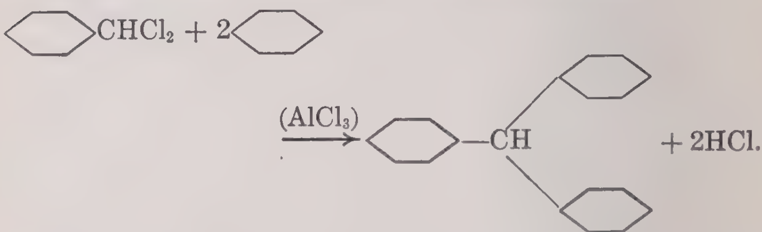
The reaction does not stop when one alkyl group has been introduced into the ring. Products containing two, three, or more side chains may be formed at the same time. Separation of the products is accomplished by fractional distillation or crystallization. The halogen atom involved in the reaction must be attached to an aliphatic carbon. Chlorbenzene, for example, will not react with an aliphatic hydrocarbon to form a homologue of benzene. But benzyl chloride or any aromatic compound having chlorine or bromine in an aliphatic side chain

* Friedel and Crafts, *Ber.*, **10**, 1180 (1877); *Compt. rend.*, **84**, 1392 (1877).

will respond to this treatment; thus benzyl chloride and benzene yield diphenyl-methane:



Benzal chloride and benzene yield triphenylmethane:



2. *Side chains removed.* A solution of xylene in benzene, when boiled with dry aluminum chloride, is partly converted into toluene. The reaction is reversible, toluene being partly converted into a mixture of xylene and benzene:

$$C_6H_4(CH_3)_2 + C_6H_6 \underset{}{\overset{(AlCl_3)}{\rightleftarrows}} 2C_6H_5CH_3.$$

3. *Formation of ketones.* Acid chlorides (aliphatic or aromatic) react with aromatic hydrocarbons to yield ketones:

$$CH_3 \cdot COCl + C_6H_6 \xrightarrow{(AlCl_3)} CH_3 \cdot CO \cdot C_6H_5 + HCl.$$

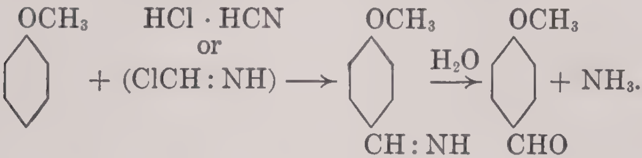
Phosgene reacts in the same way:

$$CO\begin{matrix}/Cl \\ \backslash Cl\end{matrix} + 2C_6H_6 \xrightarrow{(AlCl_3)} CO\begin{matrix}/C_6H_5 \\ \backslash C_6H_5\end{matrix} + 2HCl.$$

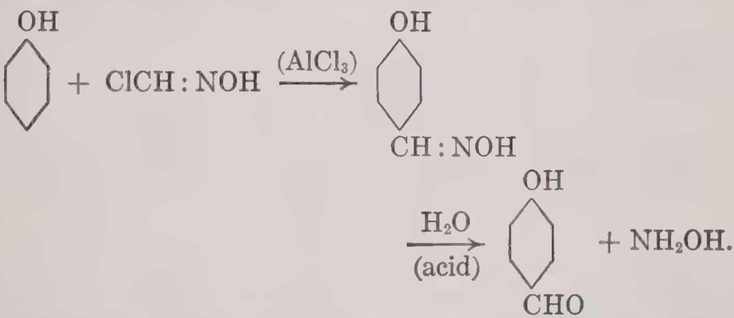
4. *Preparation of aldehydes.* A mixture of carbon monoxide and hydrogen chloride acts as if it were formyl chloride and, like any acid chloride, condenses with an aromatic hydrocarbon:

A very successful method for introducing an aldehyde group into a phenol, or a phenol ether, consists in treating the compound with a mixture of hydrogen chloride and hydrogen

cyanide gases in the presence of aluminum chloride. The condensation product is hydrolyzed by acidifying and distilling with steam:



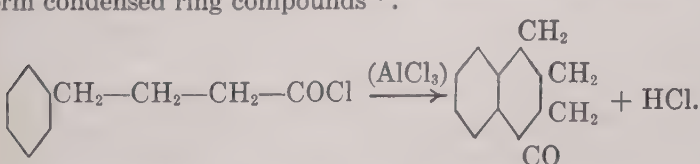
The oxime of chloroformic aldehyde serves also to introduce an aldehyde group:



Chlorformamide may be used to make the corresponding acids:

$$C_6H_6 + ClCONH_2 \longrightarrow C_6H_5CONH_2 \xrightarrow[\text{(alkali)}]{H_2O} C_6H_5COOH.$$

5. *Internal condensation.* Some aromatic compounds (especially acid chlorides) having a halogen attached to the third, fourth, or fifth carbon atom in an aliphatic side chain will form condensed ring compounds *:



6. *Chlorination.* Benzene and its homologues may be chlorinated with great rapidity by passing chlorine into a suspension of dry aluminum chloride in the hydrocarbon:

$$C_6H_6 + Cl_2 \longrightarrow C_6H_5Cl + HCl.$$

* Kipping and Hall, *Proc. Chem. Soc.*, **15**, 173 (1899).

7. *Sulphinic acids.* Benzene absorbs sulphur dioxide in the presence of aluminum chloride, forming an addition product, sulphinic acid:

$$C_6H_6 + SO_2 \longrightarrow C_6H_5SO_2H.$$

8. *Dehydration.* Aluminum chloride is a good dehydrating agent, and when a reaction mixture presents the possibility of splitting out either water or a halogen acid, the course that will be followed cannot be predicted. Trichloracetaldehyde, for example, reacts with benzene as follows:

$$CCl_3CHO + 2C_6H_6 \xrightarrow{(AlCl_3)} CCl_3CH(C_6H_5)_2 + H_2O.$$

An addition product also appears:

$$CCl_3CHO + C_6H_6 \longrightarrow CCl_3 \cdot CHOH \cdot C_6H_5.$$

And in smaller quantities, a product resulting from loss of hydrogen chloride is formed.

$$CCl_3CHO + C_6H_6 \longrightarrow C_6H_5CCl_2CHO + HCl.$$

The mechanism of the Friedel and Crafts reaction is not thoroughly understood. An intermediate product may be formed by the action of aluminum chloride on the hydrocarbon, and this, in turn, may act upon the halogen compound:

$$C_6H_6 + Al_2Cl_6 \longrightarrow C_6H_5Al_2Cl_5 + HCl;$$
$$C_6H_5Al_2Cl_5 + RCl \longrightarrow C_6H_5R + Al_2Cl_6.$$

The objection to this theory is that a large quantity of the salt is required, the yield, in most cases, being roughly proportional to the amount of aluminum chloride used. This would not be true if the salt, in the rôle of a true catalyst, could be used repeatedly. Gustavson found that aluminum chloride forms fairly stable compounds with hydrocarbons. He isolated products having the formulas $Al_2Cl_6 \cdot C_6H_6$ and $Al_2Cl_6 \cdot 6C_6H_6$. Combination of the salt with the solvent would result in its rapid removal from the field of action, and this may account for the necessity of using large quantities. On this basis, Steele * supports the claim that aluminum chloride is a true catalyst, and he maintains that it differs from other catalysts only on account of its tendency to become inactive through the formation of stable compounds of the types mentioned.

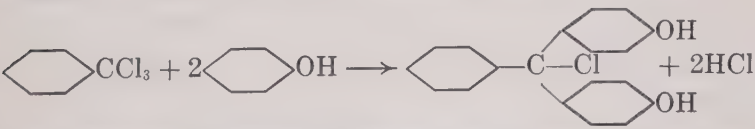
* Steele, *Trans. Chem. Soc.*, **83**, 1470 (1903).

OTHER CONDENSATIONS*

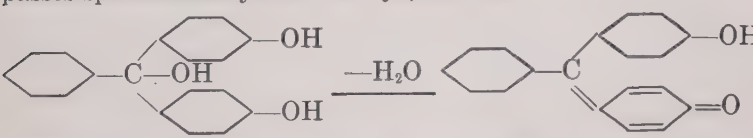
Eliminating hydrogen chloride. It is not always necessary to supply a catalyst to secure condensation through elimination of hydrogen chloride. The reaction proceeds spontaneously in many cases. Michler's ketone is prepared by the direct action of phosgene on dimethylaniline:

$$CO\begin{matrix}\diagup Cl\\ \diagdown Cl\end{matrix} + \begin{matrix}C_6H_5N(CH_3)_2\\ C_6H_5N(CH_3)_2\end{matrix} \longrightarrow CO\begin{matrix}\diagup C_6H_4N(CH_3)_2\\ \diagdown C_6H_4N(CH_3)_2\end{matrix} + 2HCl.$$

Phenol condenses in the same way with benzotrichloride:



This chloride is hydrolyzed by water, and the resulting carbinol passes spontaneously into the dye, aurine:



Eliminating water. Reactions involving the removal of water are usually carried out in the presence of dehydrating agents. Among the best reagents are phosphoric acid, sulphuric acid, aluminum chloride, zinc chloride, hydrogen chloride, acetic anhydride, and potassium hydrogen sulphate. Many reactions of this type were mentioned in the earlier chapters, and only a few examples will be reviewed here.

Cold, dilute sulphuric acid removes water from benzyl alcohol and benzene, forming diphenylmethane:

$$C_6H_5 \cdot CH_2OH + C_6H_6 \longrightarrow C_6H_5 \cdot CH_2 \cdot C_6H_5 + H_2O.$$

Diphenyl carbinol and benzene yield triphenylmethane when heated to 140° with phosphorus pentoxide:

$$\begin{matrix}C_6H_5\diagdown\\ C_6H_5\diagup\end{matrix}CHOH + C_6H_6 \longrightarrow \begin{matrix}C_6H_5\diagdown\\ C_6H_5\diagup\end{matrix}C\begin{matrix}\diagup C_6H_5\\ \diagdown H\end{matrix} + H_2O.$$

* Cohen defines condensation as "the union of two or more organic molecules or parts of the same molecule, with or without elimination of component elements, in which the new combination is effected between carbon atoms." The term, therefore, applies to a great variety of synthetic processes. Typical examples of con-

Many other alcohols and aromatic hydrocarbons condense in the same way.

Amines and phenols are especially active. A mild dehydrating agent such as hydrogen chloride, at temperatures attainable on a water bath, will cause some of them to condense with alcohols, aldehydes, and ketones. In this way the leucobase of crystal violet may be made:

$$\left.\begin{array}{l}(CH_3)_2NC_6H_4\\(CH_3)_2NC_6H_4\end{array}\right\rangle CHOH + C_6H_5N(CH_3)_2$$

$$\longrightarrow \left.\begin{array}{l}(CH_3)_2NC_6H_4\\(CH_3)_2NC_6H_4\end{array}\right\rangle C\left\langle\begin{array}{l}H\\C_6H_4N(CH_3)_2\end{array}\right. + H_2O.$$

Concentrated hydrochloric acid is used to condense acetone with phenol:

$$\left.\begin{array}{l}CH_3\\CH_3\end{array}\right\rangle CO + 2C_6H_5OH \longrightarrow \left.\begin{array}{l}CH_3\\CH_3\end{array}\right\rangle C\left\langle\begin{array}{l}C_6H_4OH\\C_6H_4OH\end{array}\right. + H_2O.$$

Zinc chloride at 120° is employed to bring about a similar reaction with diphenyleneketone:

$$\left.\begin{array}{l}C_6H_4\\ \vert\\C_6H_4\end{array}\right\rangle CO + 2C_6H_5OH \longrightarrow \left.\begin{array}{l}C_6H_4\\ \vert\\C_6H_4\end{array}\right\rangle C\left\langle\begin{array}{l}C_6H_4OH\\ \\C_6H_4OH\end{array}\right. + H_2O.$$

In this connection the preparation of phenolphthalein (p. 328) should be reviewed.

Eliminating carbon dioxide. The electrolysis of the salts of organic acids affords a suitable method for making a variety of condensation products. The metal is removed at the cathode and carbon dioxide is evolved at the anode. Sodium acetate yields ethane:

$$2CH_3COONa \rightleftarrows 2CH_3CO\bar{O} + 2\overset{+}{Na};$$

$$2CH_3CO\bar{O} - 2\,e \underset{\text{At the anode}}{\longrightarrow} CH_3 \cdot CH_3 + 2CO_2{}^*;$$

$$2\overset{+}{Na} + 2\,e + 2H_2O \underset{\text{At the cathode}}{\longrightarrow} 2NaOH + H_2.$$

densation are Würtz's synthesis, Perkin's synthesis, the Grignard reaction, Friedel and Crafts reaction, and so on.

* The symbol *e* is used to represent a unit negative charge, that is, one electron, the atom of negative electricity. Each negative ion delivers an electron to the anode, then breaks up into CO_2 and CH_3. Each sodium ion receives an electron from the cathode. It thus becomes an ordinary neutral sodium atom. It immediately decomposes water, liberating hydrogen.

If malonic acid is half neutralized with potassium hydroxide and half esterified, and then electrolyzed, the chief products formed are succinic ester and carbon dioxide:

$$\begin{array}{l} COOK \\ | \\ CH_2 \\ | \\ COOR \end{array} \longrightarrow \begin{array}{l} COO^- \\ | \\ CH_2 \\ | \\ COOR \end{array} + K^+;$$

$$2\begin{array}{l} COO^- \\ | \\ CH_2 \\ | \\ COOR \end{array} - 2e \longrightarrow 2CO_2 + \begin{array}{l} COOR \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ COOR \end{array};$$

$$2K^+ + 2e + H_2O \longrightarrow 2KOH + H_2.$$

The formation of a ketone by distilling a salt of a carboxylic acid is another example of condensation through loss of carbon dioxide:

$$2R \cdot COONa \longrightarrow R \cdot CO \cdot R + \underset{(Na_2O\,+\,CO_2)}{Na_2CO_3}.$$

Eliminating hydrogen. When benzene is passed through a red hot tube, biphenyl is formed and hydrogen escapes.

$$2C_6H_6 \longrightarrow C_6H_5 \cdot C_6H_5 + H_2$$

The apparatus is constructed so as to return all unchanged benzene vapor to the tube for reheating. The process is continuous and constitutes a very satisfactory method for making the compound.

Potassium formate, when heated, yields potassium oxalate and hydrogen:

$$2H \cdot COOK \longrightarrow \begin{array}{l} COOK \\ | \\ COOK \end{array} + H_2.$$

The Würtz Synthesis

Metallic sodium or sodium amalgam may be used to remove halogens and effect condensation of the resulting radicals. Würtz used the reaction to build up the homologues of methane:

$$2C_2H_5I + 2Na \longrightarrow C_2H_5 \cdot C_2H_5 + 2NaI.$$

Fittig applied the same method to the synthesis of aromatic hydrocarbons:

$$2C_6H_5Br + 2Na \longrightarrow C_6H_5 \cdot C_6H_5 + 2NaBr.$$

Aliphatic side chains may be introduced into aromatic nuclei by using a mixture of aromatic and aliphatic halides:

$$C_6H_5Br + C_2H_5Br + 2Na \longrightarrow C_6H_5 \cdot C_2H_5 + 2NaBr.$$

Mixed products are formed, however, when two or more halides are present, for there are equal opportunities for the formation of at least three different compounds. In the example given above ethylbenzene, diphenyl, and butane would be formed.

Other metals may be used as condensing agents. Finely divided copper (molecular copper), prepared from copper sulphate by reduction with zinc,* removes the halogens from a mixture of chloracetic ester and brombenzene, forming phenylacetic ester. The temperature required is 180° to 200°:

$$C_6H_5Br + ClCH_2 \cdot COOR + 2Cu \longrightarrow C_6H_5 \cdot CH_2 \cdot COOR + CuCl + CuBr.$$

At 230° copper removes iodine from phenyl iodide, forming biphenyl:

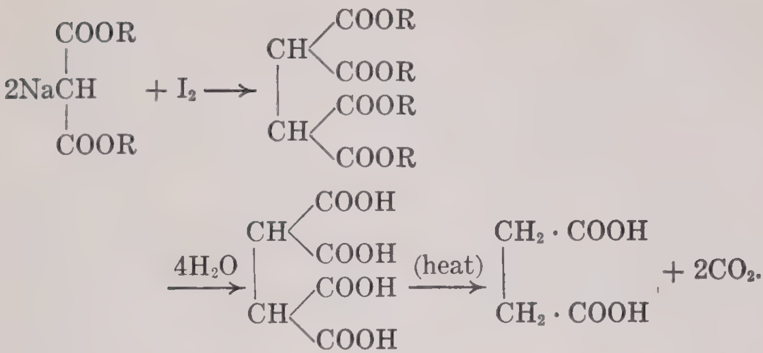
$$2C_6H_5I + 2Cu \longrightarrow C_6H_5 \cdot C_6H_5 + 2CuI.$$

Molecular silver † was used by Gomberg and his coworkers in the preparation of triarylmethyls (p. 312), and silver powder was used by Wislicenus in the preparation of adipic acid from β-iodo-propionic acid:

$$\begin{matrix} ICH_2 \cdot CH_2 \cdot COOH \\ \\ ICH_2 \cdot CH_2 \cdot COOH \end{matrix} + 2Ag \longrightarrow \begin{matrix} CH_2 \cdot CH_2 \cdot COOH \\ | \\ CH_2 \cdot CH_2 \cdot COOH \end{matrix} + 2AgI.$$

The use of a halogen to remove a metal is equally successful. Iodine acts upon sodio-acetoacetic ester, forming diethyldiacetylsuccinate (p. 390), and sodio-malonic ester responds in the same way, yielding ethane tetracarboxylic ester, a stable crystalline compound, which on hydrolysis decomposes into carbon dioxide and succinic acid:

* Gattermann, *Ber.*, **23**, 1219 (1890).
† Gomberg and Cone, *Ber.*, **39**, 3286 (1906).



The benzoin condensation. When an alcoholic solution of benzaldehyde is warmed with a small quantity of potassium cyanide it is converted almost quantitatively into benzoin.

$$2C_6H_5 \cdot CHO \longrightarrow C_6H_5 \cdot CHOH \cdot CO \cdot C_6H_5$$

The action of the cyanide ion is specific. No other catalyst for this reaction has been found. The benzoin condensation is accomplished in alkaline solution only. Free hydrocyanic acid does not furnish a sufficient concentration of cyanide ions. The reaction differs fundamentally from the aldol condensation, for it is a reaction between aldehyde groups exclusively. In the aldol condensation hydrogen migrates from the α-carbon atom of one molecule to the aldehyde group of another. In aromatic aldehydes, and in tertiary aliphatic aldehydes, no hydrogen is present on the α-carbon atom and the aldol type of condensation cannot occur. Tertiary aliphatic aldehydes and (in the absence of cyanide ions) aromatic aldehydes undergo the Cannizzaro reaction when boiled with alkalies. The reaction consists of an oxidation of half of the aldehyde molecules to the corresponding acid and simultaneous reduction of the other half to the alcohol stage. An ester is formed as an intermediate product. The mechanism by which the ester is formed is not definitely known. It appears as a condensation product of aldehyde molecules in alkaline solution. But its hydrolysis products, the free acid and alcohol, regenerate the ester only in acid solution. The Cannizzaro reaction may be represented as follows:

$$\phi \cdot CHO + \phi \cdot CHO + (KOH) \longrightarrow \phi \cdot CO \cdot O \cdot CH_2 \cdot \phi$$

$$\phi \cdot CO \cdot O \cdot CH_2 \cdot \phi \xrightarrow{H_2O} \phi \cdot COOH + \phi \cdot CH_2OH.$$

THE PERKIN REACTION

Perkin prepared cinnamic acid by heating a mixture of benzaldehyde, acetic anhydride, and sodium acetate.* He interpreted the reaction by assuming a direct condensation between the acid anhydride and the aromatic aldehyde, followed by hydrolysis of the resulting cinnamic anhydride:

$$\underset{\text{Benzaldehyde}}{2C_6H_5 \cdot CHO} + \underset{\text{Acetic anhydride}}{\begin{matrix} CH_3 \cdot CO \\ CH_3 \cdot CO \end{matrix}\!\!\!>\!O}$$

$$\longrightarrow \underset{\text{Cinnamic anhydride}}{\begin{matrix} C_6H_5 \cdot CH : CH \cdot CO \\ C_6H_5 \cdot CH : CH \cdot CO \end{matrix}\!\!\!>\!O} + 2H_2O.$$

Fittig † presented a different mechanism, based upon the assumption that it is the sodium salt and not the anhydride of the acid which combines with the aldehyde. The first step as represented by Fittig is an aldol condensation:

$$C_6H_5CHO + CH_3COONa \longrightarrow C_6H_5 \cdot CHOH \cdot CH_2 \cdot COONa.$$

Under the influence of acetic anhydride, water is eliminated, with the formation of cinnamic acid:

$$C_6H_5 \cdot CHOH \cdot CH_2 \cdot COOH \longrightarrow C_6H_5 \cdot CH : CH \cdot COOH + H_2O.$$

The net result may be indicated by a single equation:

$$C_6H_5 \cdot CHO + CH_3 \cdot COONa$$
$$\longrightarrow C_6H_5 \cdot CH : CH \cdot COONa + H_2O.$$

In support of his claim Fittig presented the following evidence:

1. Benzaldehyde condenses with sodium isobutyrate in the presence of acetic anhydride, forming phenylhydroxypivalic acid:

$$C_6H_5 \cdot CHO + H \cdot \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\dot{\underset{\cdot}{C}}}} \cdot COONa \rightarrow C_6H_5 \cdot CHOH \cdot \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\dot{\underset{\cdot}{C}}}} \cdot COONa.$$

* Perkin, *Trans. Chem. Soc.*, **31**, 389 (1877). † Fittig, *Annalen*, **216**, 115 (1882).

The reaction stops at this point, for water cannot be eliminated as it is in the case cited above.

2. Benzaldehyde, sodium propionate, and acetic anhydride, when heated to 100°, yield phenylmethylacrylic acid:

$$C_6H_5 \cdot CHO + CH_3 \cdot CH_2 \cdot COONa + (CH_3CO)_2O \longrightarrow \begin{array}{l} CH_3 \cdot C \cdot COOH + 2CH_3COOH. \\ \qquad\ \ \| \\ \qquad CH \cdot C_6H_5 \end{array}$$

The evidence is not conclusive, however, for cinnamic acid is not formed under any circumstances at 100°, and if the mixture of benzaldehyde, sodium propionate, and acetic anhydride be heated to 180°, cinnamic acid is the principal product. Nef * supported Fittig's theory, but Michael † has been able to harmonize the results of all experiments with Perkin's theory. It is obvious that in any system containing a salt of one acid and the anhydride of another, double decompositions may furnish the anhydride or the salt of either acid. There is still some uncertainty concerning the mechanism of Perkin's synthesis.

The reaction is an important one, since it affords a general method for preparing aromatic derivatives of unsaturated acids.

In the place of benzaldehyde we may substitute its homologues or the halogen, nitro-, or hydroxy-derivatives of them. Likewise, in place of acetic acid we may use the anhydride and salt of any other fatty acid, or the corresponding derivatives of dibasic acids, or even the aromatic derivatives of the monobasic and dibasic acids. Thus, phenylacetic acid and benzaldehyde yield phenylcinnamic acid:

$$C_6H_5 \cdot CHO + C_6H_5 \cdot CH_2 \cdot COOH \longrightarrow \begin{array}{l} C_6H_5 \cdot CH : C \cdot COOH \\ \qquad\qquad\quad\ \ | \\ \qquad\qquad\quad C_6H_5 + H_2O. \end{array}$$

The hydrogen removed in the formation of water is taken from the α-carbon atom. If there is only one hydrogen on the α-carbon, an aldol condensation may occur, but no water is produced; and if there is no hydrogen in the α-position, condensation fails to occur.‡

* Nef, *Ann.*, **298**, 202 (1897).

† Michael, *Am. Chem. J.*, **50**, 411 (1913).

‡ For the mechanism of similar reactions see Kohler and Corson, *J. Am. Chem. Soc.*, **45**. 1975 (1923). Kohler and Allen, *ibid.*, **45**, 1987 (1923).

Benzaldehyde, succinic anhydride, and sodium succinate yield a phenyl derivative of vinylacetic acid:

$$C_6H_5CHO + \begin{array}{l} H_2C \cdot COOH \\ \vert \\ H_2C \cdot COOH \end{array} \longrightarrow C_6H_5 \cdot CH : \begin{array}{l} C \cdot COOH \\ \vert \\ CH_2 \cdot COOH \end{array}$$
$$\longrightarrow C_6H_5 \cdot CH : CH \cdot CH_2 \cdot COOH.$$

Saturated acids are easily derived from these products. If the double bond is between the α- and β-carbon atoms, as in cinnamic acid, the addition of a halogen acid results in the formation of a β-halogen compound:

$$C_6H_5 \cdot CH : CH \cdot COOH + HBr \longrightarrow C_6H_5 \cdot CHBr \cdot CH_2 \cdot COOH.$$

With hypobromous acid, an α-halogen derivative is formed:

$$C_6H_5 \cdot CH : CH \cdot COOH + HOBr \longrightarrow C_6H_5 \cdot CHOH \cdot CHBr \cdot COOH.$$

Sodium amalgam, in water or alcohol, introduces two hydrogen atoms, potassium permanganate two hydroxyls, chlorine and bromine form addition products. It is obvious, therefore, that indirectly Perkin's reaction is useful as a means of making saturated as well as unsaturated compounds.

THE SABATIER AND SENDERENS SYNTHESIS

A process of reduction by hydrogen under the catalytic influence of a finely divided metal was developed by Sabatier and Senderens between 1897 and 1912, and since then many modifications of the reaction have been worked out by Sabatier, Mailhe, Murat, and others.

The reaction is carried out by passing a mixture of hydrogen and the vapor of the substance to be reduced over freshly reduced nickel, cobalt, copper, or iron in a heated tube. The temperature required varies with the type of compound to be reduced. Some reductions proceed smoothly and rapidly at 30°–40°, whereas other compounds must be heated to 250°–300°. By far the most efficient catalyst for most reductions is nickel. It is prepared by saturating lumps of pumice stone with a solution of nickel nitrate and heating the mass to convert the nitrate into an oxide. The pumice is then placed in a hard glass tube and heated to 320°–350°, with a stream of hydrogen passing through it. The oxide is reduced to metallic nickel. The material is not removed, but is used at once as a catalyst for gas reactions in the same tube.

Ethylene and hydrogen, in the presence of nickel, form ethane at temperatures as low as 30°–35°. At 150° the reaction is rapid. Above 300° there is considerable decomposition of ethylene resulting in deposition of carbon.

Acetylene and hydrogen combine at ordinary temperatures with an evolution of heat that may spontaneously raise the temperature of the contents of the tube to 150°. Ethane is the principal product, but small quantities of aromatic and hydroaromatic compounds are formed.

Carbon monoxide and carbon dioxide are reduced by hydrogen in the presence of nickel at 230°–250°. The reaction proceeds slowly at 180°:

$$CO + 3H_2 \longrightarrow CH_4 + H_2O;$$

$$CO_2 + 4H_2 \longrightarrow CH_4 + 2H_2O.$$

Aliphatic and aromatic nitro-compounds yield primary amines. Secondary and tertiary amines appear in smaller quantities; hydrocarbons and ammonia also are among the by-products:

$$C_6H_5NO_2 \xrightarrow{3H_2} C_6H_5NH_2 + 2H_2O;$$
$$2C_6H_5NO_2 \xrightarrow{6H_2} (C_6H_5)_2NH + NH_3 + 4H_2O;$$
$$C_6H_5NO_2 \xrightarrow{4H_2} C_6H_6 + NH_3 + 2H_2O.$$

At temperatures above 300° the benzene ring is ruptured and methane, ammonia, and water constitute the principal products.

Phenols are reduced to hydrocarbons. The reaction is slow and incomplete at 250°, and at higher temperatures there is considerable decomposition, giving rise to methane and other aliphatic bodies.

Alkyl and aryl chlorides are similarly reduced. Nickel chloride is formed during the reaction but is reconverted to metallic nickel by the excess of hydrogen. Bromides and iodides also yield hydrocarbons, but the reaction is less successful than with chlorides, probably due to the fact that nickel chloride is more readily reduced than is the bromide or iodide.

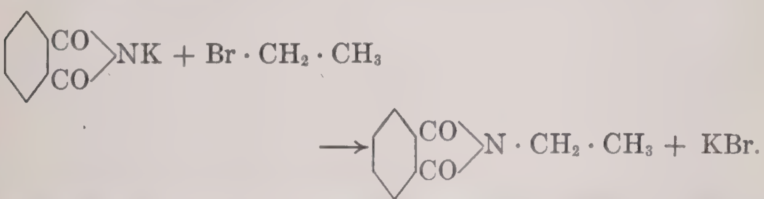
Cyanides yield amines. Primary amines predominate in the products formed, but secondary and tertiary amines and ammonia are always present:

$$RCN + 2H_2 \longrightarrow RCH_2NH_2.$$
$$2RCN + 4H_2 \longrightarrow (RCH_2)_2NH + NH_3.$$

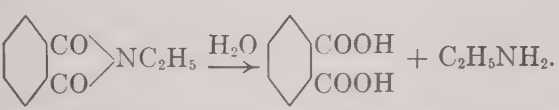
GABRIEL'S SYNTHESIS

A very useful reaction for the preparation of primary amines has been developed by Gabriel.* It consists in the treatment of a halogen compound with potassium phthalimide and subsequent hydrolysis of the resulting product.

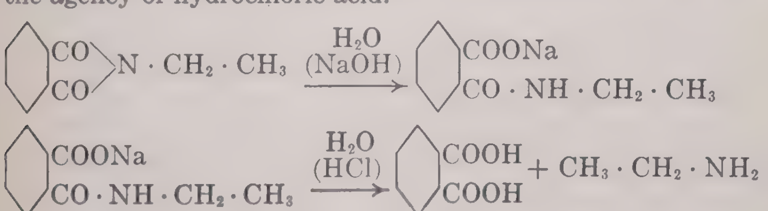
Equimolecular quantities of potassium phthalimide and an alkyl halide are heated in a sealed tube at 150°–200°, from two to five hours:



The reaction mixture is extracted with hot water to remove the potassium bromide and any excess of potassium phthalimide, and the condensation product is then hydrolyzed by boiling with an acid:



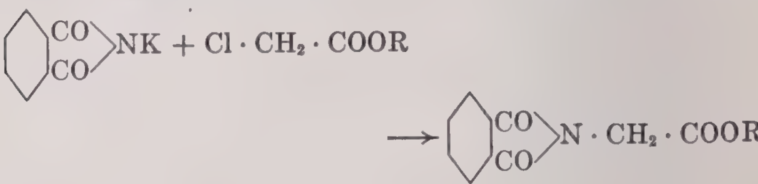
A better yield is obtained by preliminary treatment with sodium hydroxide solution which half hydrolyzes the compound. Subsequent completion of the process is then accomplished through the agency of hydrochloric acid.

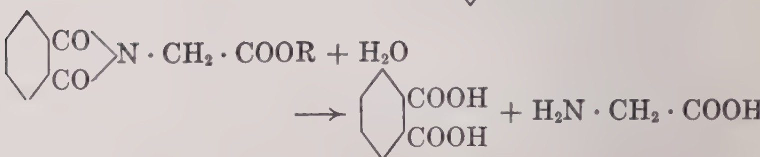


* Gabriel and Hendess, *Ber.*, **20**, 2869 (1887). Gabriel, *ibid.*, **47**, 3035 (1914); *ibid.*, **51**, 1493, 1500 (1918).

Valuable applications of the reaction were made by Sorensen* and by Fischer† in synthesizing amino acids. The methylene hydrogen in malonic ester may be replaced by halogens, and the resulting substitution products react readily with potassium phthalimide. The preparation of phenylalanine from potassium phthalimide, malonic ester, and benzyl chloride has been mentioned (p. 203).

Chloracetic ester and potassium phthalimide may be used in the preparation of glycine.





* Sorensen, *Ber.*, **41**, 3387 (1908).
† Fischer, *Ber.*, **34**, 454, 2900 (1901).

STRUCTURAL REARRANGEMENTS

Many important reactions depend upon the capacity of certain molecules, temporarily or permanently, to assume new structural forms. If the change in molecular structure is rapidly reversible, we have the phenomenon of tautomerism (p. 121). But, in many cases, compounds may be changed permanently and irreversibly into substances that bear no close resemblances to the original bodies.* Some industrial processes are based upon these rearrangements; as, for example, the preparation of benzidine from hydrazobenzene and para-aminophenol from phenylhydroxylamine.

The Beckmann Rearrangement

In 1894, Beckmann † replaced the hydroxyl group in benzophenone oxime with chlorine through the agency of phosphorus pentachloride, and the chlorine was, in turn, replaced by hydroxyl through the action of dilute alcohol and sodium hydroxide. The resulting product was not the original benzophenone oxime, but an isomeric compound — benzoyl anilid — identical with the product obtained by the action of benzoyl chloride on aniline. Beckmann assumed that the alteration in structure was accomplished by an exchange of positions between the atoms or groups attached to carbon and nitrogen, and he outlined the mechanism of the change as follows:

$$\underset{\substack{\text{Benzophenone oxime}\\ \text{I}}}{\begin{array}{c} C_6H_5-C-C_6H_5 \\ \| \\ N-OH \end{array}} \xrightarrow{PCl_5} \underset{\text{II}}{\begin{array}{c} C_6H_5-C-C_6H_5 \\ \| \\ N-Cl \end{array}} \xrightarrow{\text{rearrangement}}$$

$$\underset{\text{III}}{\begin{array}{l} C_6H_5-C-Cl \\ \qquad\;\, \| \\ \qquad\;\, N-C_6H_5 \end{array}} \xrightarrow[(C_2H_5OH)]{NaOH} \underset{\text{IV}}{\begin{array}{l} C_6H_5-C-OH \\ \qquad\;\, \| \\ \qquad\;\, N-C_6H_5 \end{array}}$$

$$\xrightarrow{\substack{\text{hydrogen}\\ \text{shift}}} \underset{\substack{\text{Benzoylanilide}\\ \text{V}}}{\begin{array}{l} C_6H_5-C=O \\ \qquad\;\, | \\ \qquad\;\, NHC_6H_5. \end{array}}$$

* For critical discussions of the theories of molecular rearrangements see: Stieglitz, *Am. Chem. J.*, **29** 49 (1903). Jones, *ibid.*, **50**, 441 (1913). Stieglitz, *J. Am. Chem. Soc.*, **38**, 2047 (1906). Michael, *ibid.*, **42**, 782 (1920). Lachman, *ibid.*, **43**, 577 (1921).

† Beckmann, *Ber.*, **27**, 300 (1894).

His theory concerning the course of the reaction was not fully confirmed by experimental evidence, but there remained no doubt about the fact that through the action of the reagents mentioned the compound of formula I was converted into the substance represented by formula V.

Stereoisomeric oximes are now distinguished from each other by application of this reaction. There are, for example, two oximes of phenyltolyl ketone,

$$\begin{array}{ccc} C_6H_5-\underset{\displaystyle\|}{C}-C_6H_4CH_3 & & C_6H_5-\underset{\displaystyle\|}{C}-C_6H_4CH_3. \\ NOH & \text{and} & HON \\ \text{I} & & \text{II} \end{array}$$

Each undergoes the Beckmann change when treated with phosphorus pentachloride or with acetic anhydride and hydrogen chloride, the hydroxyl and the aryl radicals on the same side of the molecule apparently exchanging places. From formula I, *syn*-tolylphenylketoxime, we obtain benzoyltoluidide:

$$\begin{array}{lll} C_6H_5\cdot \underset{\displaystyle\|}{C}\cdot C_6H_4\cdot CH_3 & \longrightarrow & C_6H_5\cdot \underset{\displaystyle\|}{C}\cdot OH \\ \quad\;\; NOH & & \qquad\;\; N\cdot C_6H_4\cdot CH_3 \\ & \longrightarrow & C_6H_5\cdot \underset{\displaystyle|}{CO} \\ & & \qquad\;\; NH\cdot C_6H_4\cdot CH_3. \end{array}$$

From II, *syn*-phenyltolylketoxime or *anti*-tolylphenylketoxime, we obtain toluylanilide:

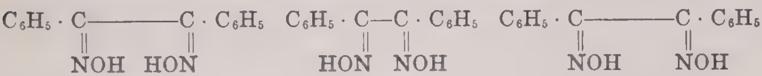
$$\begin{array}{lll} C_6H_5\cdot \underset{\displaystyle\|}{C}\cdot C_6H_4\cdot CH_3 & \longrightarrow & HO\cdot \underset{\displaystyle\|}{C}\cdot C_6H_4\cdot CH_3 \\ \quad HON & & C_6H_5\cdot N \\ & \longrightarrow & O:\underset{\displaystyle|}{C}\cdot C_6H_4\cdot CH_3. \\ & & C_6H_5\cdot NH \end{array}$$

Similarly, the two oximes derived from *p*-methoxy-benzophenone, $CH_3O\cdot C_6H_4\cdot CO\cdot C_6H_5$, are converted into substituted amides, as represented by the equations:

$$\begin{array}{lll} CH_3O\cdot C_6H_4\cdot \underset{\displaystyle\|}{C}\cdot C_6H_5 & \longrightarrow & CH_3O\cdot C_6H_4\cdot \underset{\displaystyle|}{C}:O \\ \qquad\qquad\quad NOH & & \qquad\qquad\quad NH\cdot C_6H_5 \\ \text{syn-Phenylanisylketoxime (m.p. 137°)} & & \text{Anisic anilid} \\ CH_3O\cdot C_6H_4\cdot \underset{\displaystyle\|}{C}\cdot C_6H_5 & \longrightarrow & C_6H_5\cdot \underset{\displaystyle|}{C}:O \\ \qquad\qquad HON & & \qquad NH\cdot C_6H_4\cdot OCH_3. \\ \text{anti-Phenylanisylketoxime (m.p. 116°)} & & \text{Benzoic anisid} \end{array}$$

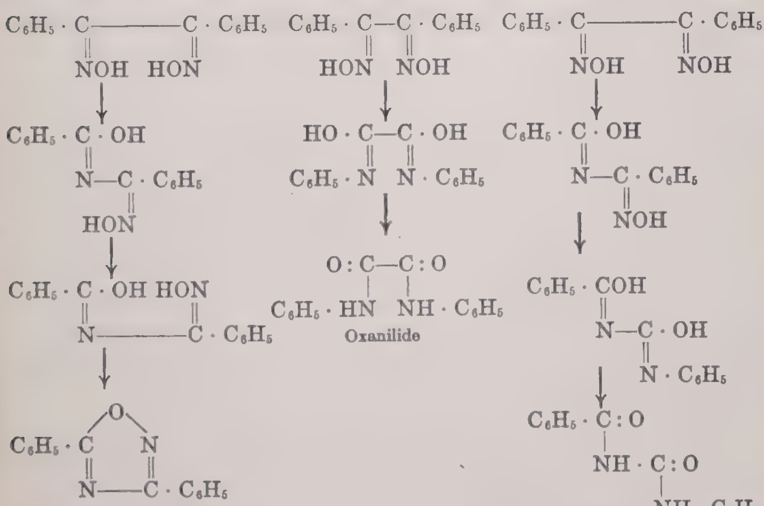
The final product is identified by hydrolysis. Anisic anilid, for example, yields anisic acid and aniline, whereas benzoic anisid is hydrolyzed to benzoic acid and anisidine.

The diketone, benzil, $C_6H_5 \cdot CO \cdot CO \cdot C_6H_5$, yields two monoximes and three dioximes. The dioximes are:



(α) m.p. 237° (β) m.p. 207° (γ) m.p. 166°

When the Beckmann change is induced through the agency of phosphorus trichloride or acetyl chloride, the α-compound yields dibenzylazoxime, due to the elimination of water after rearrangement has occurred with one of the oxime groups. The β-compound yields oxanilide, both groups undergoing the rearrangement, while the γ-isomer yields benzoylphenylurea. These changes are indicated by the following formulas:



Dibenzylazoxime Oxanilide Benzoylphenylurea

Mixed aliphatic aromatic ketones, such as acetophenone, $CH_3 \cdot CO \cdot C_6H_5$, do not yield stereoisomeric oximes. This is apparently due to the fact that the aromatic radical has a stronger influence than has the alkyl group upon the orientation of the hydroxylamine molecule, when the latter acts upon the ketone to produce an oxime. The hydroxyl group invari-

ably appears on the same side of the molecule with the aryl group. Recent experiments indicate that, in the rearrangement of an oxime, the radical in the *anti* position may be the one that migrates. (See Meisenheimer and Meis, *Ber.*, **57 B**, 289 (1924); also Auwers and Jordan, *Ber.*, **58 B**, 26 (1925).) Hantzsch listed the following groups in the order of their capacities to attract the hydroxyl in oxime formation, and pointed out the fact that in all known isomeric ketoximes the two radicals attached to the carbonyl group fall very close together in this list.

1. $CH_2 \cdot COOH$
2. $CH_2 \cdot CH_2 \cdot COOH$
3. $COOH$
4. C_6H_5
5. C_6H_4X (*m* or *p*)
6. COC_6H_5
7. C_6H_4X (*ortho*)
8. C_4H_3S
9. C_nH_{2n+1} $(n > 1)$
10. CH_3

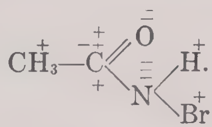
The conversion of an amide to an amine by means of a solution of bromine and potassium hydroxide, the decomposition of an acid azide by hot alcohol, yielding nitrogen and a urethane, and the conversion of an oxime into an amide are all regarded by Stieglitz as reactions of the same type as the Beckmann rearrangement. In every case, the change comprises the migration of an alkyl or aryl radical from carbon to nitrogen. The reagents that cause the rearrangement in the brom- or chlor-amides are those that have strong affinity for halogen acids, such as sodium and potassium hydroxides, and if the amide is so constituted that no halogen acid can be split off, then no rearrangement occurs. Dehydrating agents (PCl_5, CH_3COCl, etc.) cause the change in oximes, and heat alone liberates nitrogen from azides.

The mechanism of the rearrangement, as outlined by L. W. Jones, in harmony with Stieglitz's views concerning the formation of an intermediate derivative of univalent nitrogen, may be stated as follows:* Taking as an example the conversion of acetamide into methyl amine, we have first the replacement of amino hydrogen by bromine.

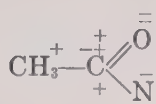
$$CH_3 \cdot CO \cdot NH_2 + Br_2 + KOH \longrightarrow CH_3 \cdot CO \cdot NHBr + KBr + H_2O$$

* Jones, *Am. Chem. J.*, **48**, 1 (1912). Stieglitz, *ibid.*, **18**, 751 (1896). Stieglitz and Slosson, *ibid.*, **29**, 289 (1903). Stieglitz and Peterson, *Ber.*, **43**, 782 (1910). Stieglitz and Leech, *J. Am. Chem. Soc.*, **36**, 272 (1915).

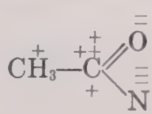
The bromine used is the positive ion of hypobromous acid. The substitution cannot be made by using hydrobromic acid, phosphorus tribromide, or any other source of the negative bromide ion. On hydrolysis in acid solution the bromamide regenerates HOBr. Hence it is assumed that the electronic structure of the bromamide is



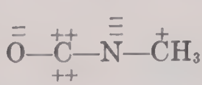
In the presence of a strong base this compound loses HBr. But before this can happen the positive bromine must become a bromide ion through acquisition of two electrons. The electrons are drawn from the nitrogen, leaving an unstable intermediate compound of univalent nitrogen.



When this state is reached, the unsaturated nitrogen draws two electrons from the carbon to which it is attached, forming



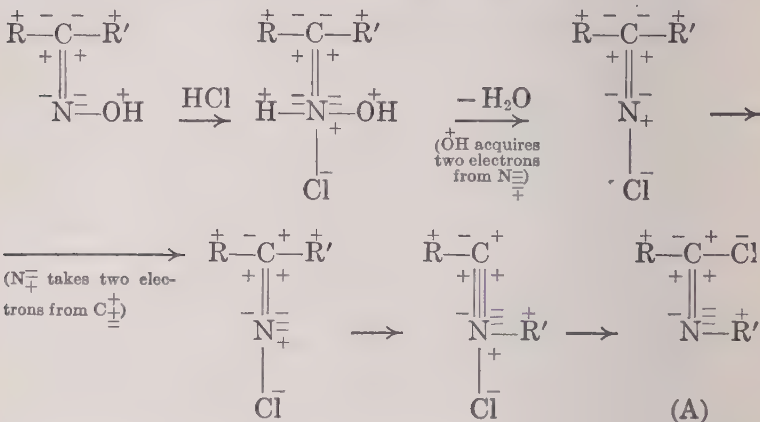
This change in the polar character of the carbon atom renders it unable to retain the positive alkyl radical and the latter migrates to the more strongly negative nitrogen, yielding the isocyanate



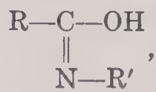
The isocyanate is hydrolyzed to an amine, CH_3NH_2, and carbon dioxide.

Dehydrating agents cause the Beckmann change in ketoximes, and Stieglitz assumes, therefore, that the intermediate compound of univalent nitrogen is formed through loss of water. This is possible if the oxime first forms an addition product with hydrogen chloride which is present when the

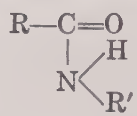
reaction is induced by means of phosphorus trichloride, acetyl chloride, or by acetic acid saturated with hydrogen chloride.



By hydrolysis this product (A) yields



which immediately changes to the substituted amide



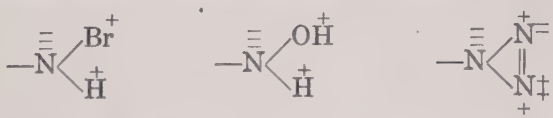
There is at least one objection to the mechanism outlined above. The chlorimido ketones, R—C—R′, formed by the
‖
N—Cl

action of hypochlorous acid on the corresponding imides, do not undergo the Beckmann rearrangement. Stieglitz calls attention to the fact that the chlorimido ketones are derivatives of hypochlorous acid in which the chlorine is positive and that the oxime salts having the same structure are derivatives of hydrochloric acid in which the chlorine is negative.

If compounds having identical atomic structures can have different distributions of electrical charges, there exists the possibility of electronic isomerism. That is to say, there may be compounds that are isomers by virtue of differences in

electronic structures. L. W. Jones has presented evidence in support of the belief that such isomers exist. They are called electromers.*

In every example of the Beckmann rearrangement the process involves reduction of nitrogen and oxidation of carbon.† In every case, according to Stieglitz, nitrogen is attached to an atom or group which must acquire two electrons in order to function in its usual stable ionic form. In the following typical examples the capacity of bromine, hydroxyl, and nitrogen to acquire electrons is indicated by the plus sign.



The rearrangement starts by an absorption of two electrons by these groups which are relatively positive. It is assumed that the electrons are drawn from the nitrogen in the first instance, but that ultimately the carbon atom to which the nitrogen is attached is oxidized by loss of electrons, this step being followed by the shift of a positive group from carbon to nitrogen.

The use of a bond having one end positive and the other negative (a polar bond) has been avoided in this text except in the presentation of special theories that are based upon this conception of valence. Elements differ in their capacities to attract and hold electrons, and in any compound electrons may be drawn closer to some atoms than to others. Any unsymmetrical distribution of electrons means that some elements are more positive or more negative than others. But it is not necessary to assume a complete transfer of an electron from one atom to another in a non-electrolyte, nor is it necessary to assume that because an atom enters into combination as a positively charged particle that the state of this atom in the compound is different from what it would be if it had been negatively charged at the time combination occurred. The author believes that any two molecules having the same composition and the same structural arrangement of the atoms are identical. The previous history of the atoms that have entered into the structure can be ignored.

* L. W. Jones, *J. Am. Chem. Soc.*, **36**, 1268 (1914). W. A. Noyes, *ibid.*, **35**, 767 (1913). L. W. Jones, *Science*, **46**, 493 (1917). Arthur Michael, *J. Am. Chem. Soc.*, **42** (1920).

† L. W. Jones, *Am. Chem. J.*, **50**, 414 (1913).

Many atoms and groups function as electro-positive or as electro-negative radicals, the course of the reaction being determined by the environment. By hydrolysis in acid solution we obtain from benzenesulphonic acid, benzene and sulphuric acid. By fusing the same compound with an alkali we obtain phenol and a salt of sulphurous acid. It does not follow that there are two benzenesulphonic acids (electromers), in one of which the phenyl group is positive and in the other negative. Benzenesulphonic acid dissociates as follows:

$$C_6H_5{:}SO_3H \left\langle \begin{array}{l} \xrightarrow{\text{in acid}} \overset{-}{C_6}H_5{:} + \overset{+}{S}O_3H \\[2ex] \xrightarrow{\text{in alkali}} \overset{+}{C_6}H_5 + {:}\overset{-}{S}O_3H \end{array} \right.$$

The environment determines which of the groups shall have possession of an extra electron; but these groups are not independently electrically charged in the undissociated compound.

Chlorine must be in an electro-positive condition, as derived from hypochlorous acid, for the replacement of hydrogen on nitrogen in an amine; but after the halogen has formed its union with the nitrogen of the amine its electrochemical character must be determined by the nature of the molecule as a whole.

A nitroparaffin is formed by the action of nitric acid upon a hydrocarbon. The same product is obtained by the action of silver nitrite on the corresponding alkyl halide. In the first instance the positive NO_2 group of nitric acid combines with an alkyl radical. In the second case the negative NO_2 group of nitrous acid combines with the same radical.

$$R \cdot H + \overset{-}{H}O \cdot \overset{+}{N}O_2 \longrightarrow R \cdot NO_2 + H_2O$$
$$R \cdot X + \overset{+}{Ag} \cdot \overset{-}{N}O_2 \longrightarrow R \cdot NO_2 + AgX$$

The products are not electromers; they are identical.

THE PINACOL REARRANGEMENT

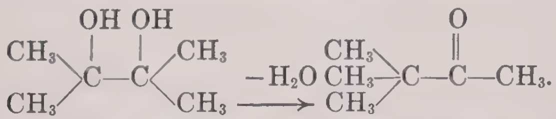
The reduction of acetone results in the production of isopropyl alcohol, $CH_3 \cdot CHOH \cdot CH_3$, and a ditertiary alcohol known as pinacol. The latter is formed by the union of two partially reduced acetone molecules:

$$\underset{\text{Acetone}}{2CH_3 \cdot CO \cdot CH_3} + 2H \longrightarrow \underset{\text{Pinacol}}{\begin{array}{c} OH \\ | \\ CH_3—C—CH_3 \\ | \\ CH_3—C—CH_3 \\ | \\ OH \end{array}}.$$

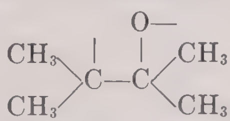
Pinacol is a colorless, crystalline substance (m.p. 42°, b.p. 172°), soluble in hot water, from which, on cooling, it crystallizes with six molecules of water. When warmed with dilute sulphuric acid or phosphoric acid or even when heated alone, pinacol undergoes a rearrangement that gives rise to a colorless liquid called pinacolone,* an unsymmetrical ketone,

$$(CH_3)_3C \cdot CO \cdot CH_3.$$

The change involves the migration of a methyl group from one carbon to another, with concomitant loss of water:

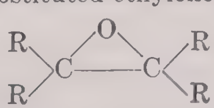


Many theories have been advanced to account for this change. Tiffeneau† assumes that dehydration is the first step in the process, the intermediate product being an unstable, unsaturated body, represented by the formula:



The second step he maintains is the migration of a methyl group from the carbon which retains an oxygen atom to the adjacent carbon.

An intermediate product of the type given above could very easily give rise to a substituted ethylene oxide,



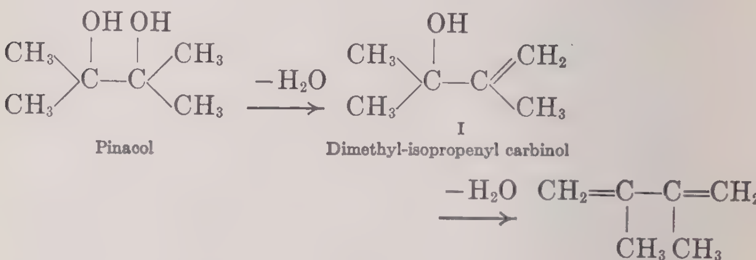
and in some cases there is evidence of the formation of the oxide. But nearly all of the well-known ethylene oxides are very readily hydrated, forming the corresponding glycols, and it is not likely that such oxides would appear in dilute aqueous solutions as dehydration products of pinacols.

Lachman assumes that the first step comprises a shift of a hydroxyl group, placing both hydroxyl groups, temporarily, on the same carbon atom. This is followed by migration of

* Pinacol and pinacolone were formerly called pinacone and pinacoline, respectively.

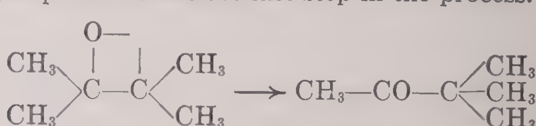
† Tiffeneau, *Ann. Chim. Phys.*, **10** (series 8), 330 (1907).

a methyl group to the position vacated by the hydroxyl, and finally the dihydroxy compound loses water, forming the ketone.* A similar view was held by Lieben† and by Kondakow.‡ Michael§ has a different theory. It is well known that tertiary alcohols are easily dehydrated by dilute mineral acids. They yield unsaturated hydrocarbons. In accord with this general behavior pinacol, being a ditertiary alcohol, should yield two products as follows:



Pinacol — I Dimethyl-isopropenyl carbinol — II 2, 3-Dimethylbutadiene

Now, 2, 3-dimethylbutadiene is regularly formed as a by-product in the pinacol rearrangement, and, therefore, dehydration of pinacol occurs as indicated. In the dimethyl-isopropenyl carbinol (I) it will be observed that the hydroxyl hydrogen and the methylene carbon are very close together (that is, they are in 1, 5 positions. See p. 130). Michael points out that the spatial arrangement is such that it involves almost no change in position for the hydrogen to leave the oxygen and become attached to the methylene carbon. This gives rise to an unsaturated body of the type suggested by Tiffeneau, and migration of the methyl group constitutes the last step in the process.

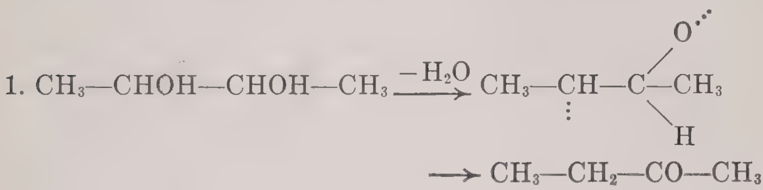


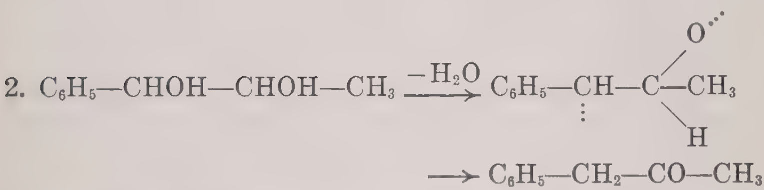
Whatever the mechanism of the pinacol rearrangement may be, the example given above is but a single illustration of a very general reaction. Most of the 1, 2-glycols (dihydric alcohols with the hydroxyl groups on adjacent carbon atoms) are readily

* Lachman, *J. Am. Chem. Soc.*, **44**, 338 (1922).
† Lieben, Monatsh, **23**, 60 (1902).
‡ Kondakow, *Chem. Zentr.*, 1120 (1899).
§ Michael, *J. Am. Chem. Soc.*, **42**, 803 (1920).

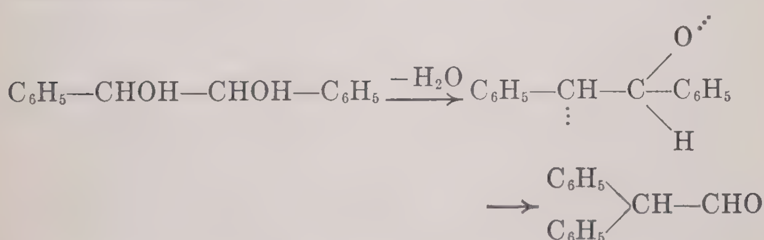
converted into aldehydes or ketones, and this conversion involves an intramolecular rearrangement.

Disecondary 1, 2-glycols form ketones through the migration of hydrogen and loss of water.





In a few instances an aromatic radical rather than hydrogen makes the shift.



An analogous result has not been observed in the aliphatic series. An alkyl radical never shifts its position if there is a hydrogen atom attached to the same carbon.

The Benzil Rearrangement

Benzil, a yellow, crystalline diketone, $C_6H_5 \cdot CO \cdot CO \cdot C_6H_5$, which melts at 95° and boils with decomposition at 347°, is converted by hot aqueous alkali into a salt of benzilic acid:

$$C_6H_5 \cdot CO \cdot CO \cdot C_6H_5 \xrightarrow{KOH} (C_6H_5)_2C(OH) \cdot COOH.$$

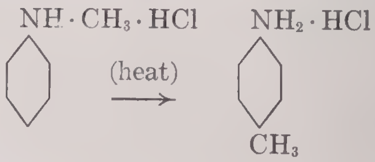
No thoroughly tested and satisfactory explanation of the change has been offered. For discussions of various theories

relating to this reaction, the student is directed to papers by Nicolet and Pelc,* Michael,† Schroter,‡ Nef,§ and Lachman.**

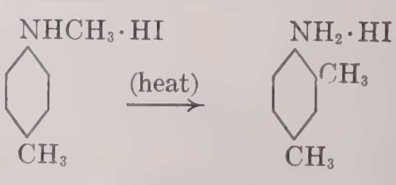
THE HOFMANN REARRANGEMENT

Two intramolecular rearrangements were discovered by Hofmann; the conversion of an amide into an amine, and the formation of *para*-toluidine from methyl aniline. The first of these reactions is discussed under the Beckmann rearrangement, for it is an example of the same type of change that Beckmann discovered in connection with the oximes. The second reaction will be considered now, and many similar reactions not mentioned in Hofmann's paper will be placed in the same category.

When monomethyl aniline is treated with hydrochloric acid, in sufficient quantity to form the hydrochloride of the amine, and then heated to 150°, the methyl group migrates from the nitrogen to the para position of the ring. The hydrogen atom occupying the para position simultaneously passes to the nitrogen:

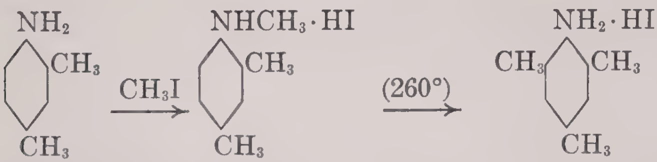


The rearrangement amounts to an exchange of places between the *para* hydrogen and the methyl group. The mechanism of the reaction may not be quite so simple as this. It is possible that the first step consists in the formation of methyl chloride and aniline. This, however, is not an established fact. Methyl iodide, bromide, or chloride will form an addition product with toluidine, which, when heated, undergoes the Hofmann rearrangement, yielding xylidine:



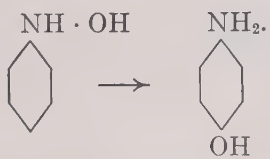
* Nicolet and Pelc, *J. Am. Chem. Soc.*, **43**, 935 (1921).
† Michael, *ibid.*, **42**, 812 (1920).
‡ Schroter, *Ber.*, **42**, 2336 (1909).
§ Nef, *Ann.*, **298**, 372 (1897).
** Lachman, *J. Am. Chem. Soc.*, **45**, 1529 (1923).

From xylidine, by the same procedure, we may obtain mesidine



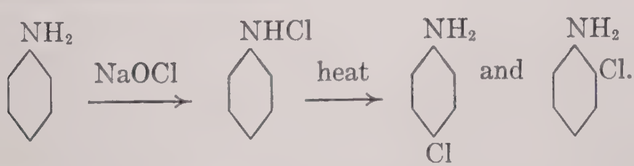
No further substitution can be accomplished by this method. A shift to the *meta* position does not take place under any circumstances.

Phenylhydroxylamine, formed by reduction of nitrobenzene in neutral solution, is converted by acids into *para*-aminophenol:

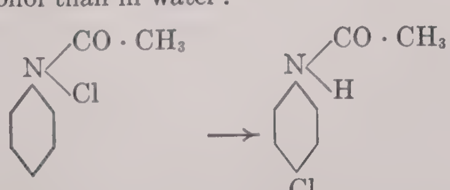


In this case, the hydroxyl group shifts from nitrogen to the *para* carbon, as does the methyl radical in methyl amines.

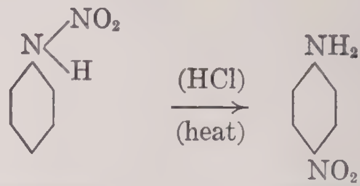
Hypochlorites react with aniline and other amines, forming chloramines. When warmed, the latter are transformed into *para*- and *ortho*-chloranilins:



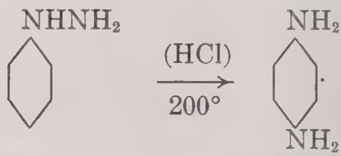
Acetylchloranilid is stable in neutral solution, but in the presence of hydrogen ions is converted into *p*-chloracetanalid. The transformation is catalyzed by light and proceeds much faster in alcohol than in water:



Other groups migrate from nitrogen to carbon, as indicated below:

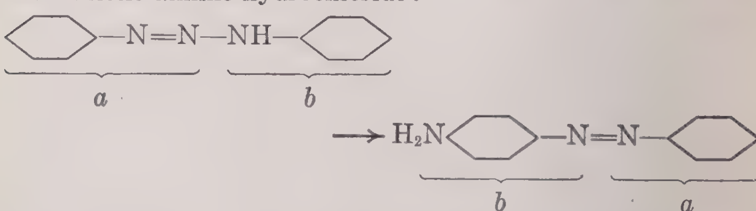


Phenylnitramine　　　　*p*-Nitroaniline



Phenylhydrazine　　　　*p*-Phenylenediamine

The conversion of diazoaminobenzene into aminoazobenzene is a typical example of this rearrangement. It is accomplished by warming a solution or aqueous suspension of the compound with a little aniline hydrochloride:



The portion of the molecule marked *a* migrates to the *para* position of the ring in the aniline residue marked *b*.

The benzidine change consists of two rearrangements brought about by warming hydrazobenzene with hydrochloric acid. The first shift gives rise to semidine and the final readjustment produces benzidine. In each case a group migrates from the nitrogen of an aromatic amine to the *para* carbon atom. (See p. 256.)

The Walden Inversion

An optically active compound is racemized usually by heat alone or by boiling with an acid or alkali. From the racemic mixture, the dextro and lævo forms may be isolated by the methods outlined under stereoisomerism (p. 136).

In 1895, Walden prepared *d*-chlorsuccinic acid from *l*-chlorsuccinic acid without racemization. The change was accom-

plished by replacing the chlorine atom by hydroxyl through the agency of silver hydroxide, then replacing the hydroxyl by chlorine through the action of phosphorus pentachloride:

$$
\begin{array}{ccccc}
\mathrm{COOH} & & \mathrm{COOH} & & \mathrm{COOH} \\
| & & | & & | \\
\mathrm{CHCl} & \xrightarrow{\mathrm{AgOH}} & \mathrm{CHOH} & \xrightarrow{\mathrm{PCl_5}} & \mathrm{CHCl} \\
| & & | & & | \\
\mathrm{CH_2} & & \mathrm{CH_2} & & \mathrm{CH_2} \\
| & & | & & | \\
\mathrm{COOH} & & \mathrm{COOH} & & \mathrm{COOH} \\
l\text{-Chlorsuccinic acid} & & l\text{-Malic acid} & & d\text{-Chlorsuccinic acid}
\end{array}
$$

Somewhere in the process outlined by these formulas a change in structure occurs. Either the hydroxyl group fails to take the position previously occupied by chlorine, or the phosphorus pentachloride fails to introduce chlorine in the position occupied by the replaced hydroxyl. The fact that the sign of the optical rotation changes as a result of the second reaction does not imply that the change in positions of the groups around the asymmetric carbon atom occurs also in this step, for there is no reason to assume that hydroxy and chlorine compounds of like structure should have similar optical properties. But when the hydroxyl group is replaced by chlorine, regenerating chlorsuccinic acid, one would expect to find either racemization or a restoration of the original optical properties. The product actually obtained is the mirror image of the original substance, and, therefore, somewhere along the line, an inversion occurs.

Silver hydroxide acts upon *d*-chlorsuccinic acid, converting it into *d*-malic acid, which in turn yields *l*-chlorsuccinic acid. We have, therefore, a complete cycle:

$$
\begin{array}{ccc}
\mathrm{COOH\cdot CHCl\cdot CH_2\cdot COOH} & \xrightarrow{\mathrm{AgOH}} & \mathrm{COOH\cdot CHOH\cdot CH_2\cdot COOH} \\
l\text{-Chlorsuccinic acid} & & l\text{-Malic acid} \\
\uparrow \mathrm{PCl_5} & & \downarrow \mathrm{PCl_5} \\
\mathrm{COOH\cdot CHOH\cdot CH_2\cdot COOH} & \xleftarrow{\mathrm{AgOH}} & \mathrm{COOH\cdot CHCl\cdot CH_2\cdot COOH} \\
d\text{-Malic acid} & & d\text{-Chlorsuccinic acid}
\end{array}
$$

If potassium hydroxide be substituted for silver hydroxide, a different malic acid is produced:

$$
l\text{-Chlorsuccinic acid} \;\underset{\mathrm{PCl_5}}{\overset{\mathrm{KOH}}{\rightleftarrows}}\; d\text{-Malic acid}
$$

Walden's experiments* revealed the fact that the weak bases Ag_2O, HOH, $TlOH$, HgO, Hg_2O, and PdO substitute hydroxyl for chlorine in chlorsuccinic acid without change of sign; that is to say, they convert *l*-chlorsuccinic acid into *l*-malic acid. The stronger bases $RbOH$, KOH, NH_4OH, $Ba(OH)_2$, $NaOH$, and $LiOH$, convert chlorsuccinic acid into malic acid of opposite sign. A reaction which involves no change in configuration is said to be normal, and one that is accompanied by a rearrangement of the groups attached to the asymmetric carbon atom is designated abnormal. But since at least two reactions are required to change a compound to its optical enantiomorph, it is difficult, if not impossible, to decide which reaction actually produces the structural modification. Fischer sought to settle the question by comparisons of the following type.

Ammonia acts the same way on brompropionic acid and on its esters, producing no change of sign in either case. Nitrosyl bromide, on the other hand, causes a change in the sign of rotation when it acts upon a free amino acid, but no change when it acts upon an ester of the same acid:

$$\underset{d\text{-Alanine}}{CH_3 \cdot CHNH_2 \cdot COOH} \xrightarrow{NOBr} \underset{l\text{-Brompropionic acid;}}{CH_3 \cdot CHBr \cdot COOH}$$

$$\underset{d\text{-Alanine ester}}{CH_3 \cdot CHNH_2 \cdot COOR} \xrightarrow{NOBr} \underset{d\text{-Brompropionic ester;}}{CH_3 \cdot CHBr \cdot COOR}$$

$$\underset{d\text{-Brompropionic acid}}{CH_3 \cdot CHBr \cdot COOH} \xrightarrow{NH_3} \underset{d\text{-Alanine;}}{CH_3 \cdot CHNH_2 \cdot COOH}$$

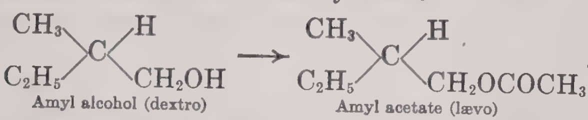
$$\underset{d\text{-Brompropionic ester}}{CH_3 \cdot CHBr \cdot COOR} \xrightarrow{NH_3} \underset{d\text{-Alanine ester.}}{CH_3 \cdot CHNH_2 \cdot COOR}$$

He concluded, therefore, that ammonia acts normally, that is, without change in configuration. Phosphorus pentachloride would be regarded as acting normally, for it gives similar results with acids and all derivatives of the acids, and in all solvents. In the case of chlorsuccinic and malic acids cited above, Fischer concluded that the change in configuration was caused by silver hydroxide, although it produced dextro-malic acid from dextro-chlorsuccinic, and that phosphorus pentachloride

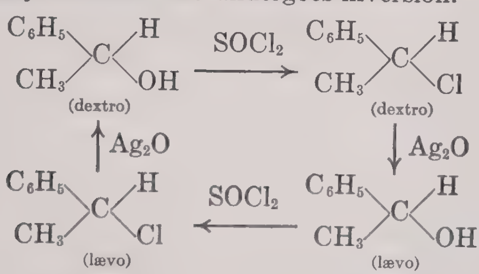
* Walden, *Ber.*, **32**, 1841 (1899).

acted without change in structure, the reversal of the sign of rotation being due entirely to substitution of chlorine for hydroxyl.

That a change in sign may be produced without altering the relative positions of groups attached to an asymmetric carbon atom, but merely by making a change in the composition of one of them, is proved by the fact that dextro-rotatory amyl alcohol yields a lævo-rotatory ester:



Most of the α-amino acids and some β-amino acids, like the α-halogen acids, are susceptible to the Walden inversion. Methyl-phenyl carbinol also undergoes inversion.



Werner and Stark assume that the first step in a substitution process involving a Walden inversion is the formation of an addition product. Potassium hydroxide, for example, acting upon brompropionic acid, is supposed to attach itself to the asymmetric atom, through residual valence, at some place between the four groups satisfying the primary valences of the carbon. Potassium bromide is then eliminated. At the moment when the halogen is released from the carbon atom, there are two possibilities: (1) the hydroxyl group may take the place of the bromine, or (2) it may retain its intermediate position, causing the three remaining groups to shift into new positions to reëstablish the tetrahedral symmetry of the molecule.

If all molecules behave according to (1), there is no inversion. If all react as indicated in (2), there is total inversion. If half of the molecules react as in (1) and half as in (2), a racemic mixture is produced. Partial racemization always occurs in these reactions, so that any explanation of inversion must present two possible mechanisms.

KOPP'S LAW

Boiling points. An inspection of the tables of physical constants, given in connection with the various classes of compounds, reveals the fact that, in any series, the boiling points become higher as the molecular weights increase. Kopp tabulated some of the physical constants (freezing points, boiling points, and densities) of many classes of compounds as early as 1842, and reached the conclusion that "equal differences in composition of organic compounds correspond to equal differences in boiling point."* This generalization, known as Kopp's law, was soon found to be unreliable. If it were an exact law, isomeric compounds would have the same boiling point, and this is almost never the case. Kopp revised his statement later, making it apply only to such compounds as have similar structural formulas. Constitution as well as composition was recognized as having an influence upon the boiling point. Thus ethyl acetate, $CH_3 \cdot CO \cdot OC_2H_5$, and butyric acid, C_3H_7COOH, are isomeric but structurally different, and there is a difference of 82° in their boiling points. Methyl acetate, $CH_3 \cdot CO \cdot OCH_3$, and ethyl formate, $H \cdot CO \cdot OC_2H_5$, on the other hand, are not only isomeric but structurally alike, and their boiling points are nearly identical (56° and 55° respectively). But even when comparisons are made between normal members of the same class, the rule is only a rough approximation.

Alcohols	B.P.		Acids	B.P.	
CH_3OH	66°		HCOOH	105°	
		12			12
C_2H_5OH	78°		CH_3COOH	117°	
		19			24
C_3H_7OH	97°		C_2H_5COOH	141°	
		20			21
C_4H_9OH	117°		C_3H_7COOH	162°	
		21			24
$C_5H_{11}OH$	138°		C_4H_9COOH	186°	
		19			19
$C_6H_{13}OH$	157°		$C_5H_{11}COOH$	205°	

* Kopp, *Annalen*, **41**, 79 (1842).

Esters	B.P.	Diff.	Alkyl Iodides	B.P.	Diff.
$HCOOC_2H_5$	55°		CH_3I	40°	
		19			32
$CH_3COOC_2H_5$	74°		C_2H_5I	72°	
		22			30
$C_2H_5COOC_2H_5$	96°		C_3H_7I	102°	
		20			27
$C_3H_7COOC_2H_5$	116°		C_4H_9I	129°	
		28			26
$C_4H_9COOC_2H_5$	144°		$C_5H_{11}I$	155°	
		70			27
$C_5H_{11}COOC_2H_5$	214°		$C_6H_{13}I$	182°	

These tables afford the best support that can be found for Kopp's rule. The hydrocarbons and many other classes of compounds show even greater deviations.

Walker used the formula,

$$T = aM^b$$

for calculating the boiling points of hydrocarbons. In this formula T is the absolute boiling point of a hydrocarbon of molecular weight, M and a and b are constants. For the methane series $a = 37.38$ and $b = 0.5$.

Such an equation cannot give an exact value, for it fails to take into account molecular structure. The boiling point and every other physical and chemical property of a compound is a function not only of molecular weight and composition, but also of the internal forces that determine the orientation of the atoms within the molecule. Until these forces are fully understood and accurately estimated we cannot hope to formulate a mathematical expression that will make possible a precise calculation of any physical constant.

Some attempts have been made to express the boiling point of a compound as the sum of values attributable to various groups, such as (1) methylene, (2) methyl, (3) carboxyl, (4) hydroxyl, (5) carbonyl, (6) amino, and so on. By assigning to each of these a definite constant value of such magnitude as is necessary to make their sums represent the actual boiling points of a number of known compounds, an equation may be written that gives approximately true results when applied to new compounds. As an example of attempts that have been made in this direction, the student is referred to the work of Casale.*

Molecular volumes. The volume occupied by the molecular weight of a liquid is a function of its composition and of its

* *Atti. acad. Sci.*, Torino, **50**, 809 (1915).

molecular structure. In the following table of normal alcohols, V, the molecular volume, $\left(\frac{M}{d}\right)$, is based upon the density of the substance at 0°.

Alcohol	M	d	V	Difference
CH_3OH	32	0.812	39.4	
C_2H_5OH	46	0.806	57.1	17.7
C_3H_7OH	60	0.817	73.4	16.3
C_4H_9OH	74	0.823	89.9	16.5
$C_5H_{11}OH$	88	0.829	106.1	16.2
$C_6H_{13}OH$	102	0.833	122.5	16.4
$C_7H_{15}OH$	116	0.836	138.7	16.2
$C_8H_{17}OH$	130	0.839	154.9	16.2
$C_9H_{19}OH$	144	0.842	171.1	16.2

The molecular volume of CH_2 is, therefore, 16.2 cc. in the series of normal saturated alcohols at 0°. Such constancy, however, is not found in all series, and Kopp concluded that the arbitrary adoption of a definite temperature (such as 0° C.) was illogical. He maintained that liquids were in "corresponding states" at their boiling points, and that a comparison of molecular volumes of the alcohols at their boiling points would be the best method for determining the increment in molecular volume due to an increase of CH_2 in composition. The molecular volume of methyl alcohol at 66°, for example, should be compared with that of ethyl alcohol at 78.4°. With this change in the method, fairly constant differences were found in all homologous series, with approximately the same value for CH_2, namely, 22 cc., regardless of the class of compounds considered. Molecular volume, therefore, was assumed to be an additive property of liquids.

At least one important contribution to this theory has been made since Kopp's time. Instead of selecting the boiling points as representing corresponding states, comparisons are now made at temperatures representing equal fractions of the absolute critical temperatures of the substances and under pressures that represent equal fractions of their critical pressures.* The measured volume, v, of a liquid or gas divided by its critical volume, ϕ_0, is called the reduced volume, ϕ; its actual absolute

* The critical temperature of a substance is the temperature above which it cannot be liquefied by the application of pressure. Its critical pressure is the pressure required to liquefy the vapor of the substance at the critical temperature. The critical volume is the volume of one mol of the substance at the critical temperature and under the critical pressure.

temperature, T, divided by its critical temperature, θ_0, is its reduced temperature, θ; and its pressure, p, divided by its critical pressure, π_0, is its reduced pressure, π. When for any two substances π and θ are identical, the substances are in corresponding states. At the critical point there is no distinction between liquid and vapor, the boundary between the two phases disappears, and the system becomes homogeneous.

Van der Waals' equation applies to gases with fair precision, and it holds approximately for homogeneous liquids. It represents an equation of state indicating definite relations between the volume, pressure, and temperature of a substance:

$$\left(p + \frac{a}{v^2}\right)(v - b) = RT$$

or

$$v^3 - \left(b + \frac{RT}{p}\right)v^2 + \frac{a}{p}v - \frac{ab}{p} = 0.$$

Representing the three roots of v by x, y, and z, we have

$$(v - x)(v - y)(v - z) = 0.$$

At the critical point, where $v = \phi_0$, the three roots are real and equal, hence,

$$x = y = z = \phi_0$$

and

$$(v - \phi_0)^3 = v^3 - \left(b + \frac{R\theta_0}{\pi_0}\right)v^2 + \frac{a}{\pi_0}v - \frac{ab}{\pi_0}.$$

Now in any cubic equation of the form $v^3 - av^2 + bv - c = 0$, if the three roots are equal the following relation obtains between the triple root x (or, in this case, ϕ_0) and the coefficients of the various powers of v:

$$a = 3x, \quad b = 3x^2, \quad c = x^3.$$

Then

$$3\phi_0 = b + \frac{R\theta_0}{\pi_0}, \qquad 3\phi_0^2 = \frac{a}{\pi_0}, \quad \text{and} \quad \phi_0^3 = \frac{ab}{\pi_0}.$$

Solving these three simultaneous equations for ϕ_0, π_0, and θ_0, we obtain:

$$\phi_0 = 3b, \ \pi_0 = \frac{a}{27b^2}, \quad \text{and} \quad \theta_0 = \frac{8a}{27bR}.$$

Thus, the van der Waals constants, a and b, obtained from a consideration of deviations from the gas law, $PV = nRT$, may be used as a basis for calculating the critical volume, pressure,

or temperature of a liquid or gas. Conversely, if the critical values are known, the constants may be calculated.

From the above equations we have also

$$a = 3\pi_0\phi_0^2, \quad b = \frac{\phi_0}{3}, \quad R = \frac{8\pi_0\phi_0}{3\theta_0}.$$

Substituting these values in the original form of the van der Waals equation:

$$\left(p + \frac{3\pi_0\phi_0^2}{v^2}\right)\left(v - \frac{\phi_0}{3}\right) = \frac{8\pi_0\phi_0 T}{3\theta_0}.$$

Dividing both sides of the equation by $\frac{\pi_0\phi_0}{3}$:

$$\left(\frac{p}{\pi_0} + \frac{3\phi_0^2}{v^2}\right)\left(\frac{3v}{\phi_0} - 1\right) = \frac{8T}{\theta_0}.$$

According to the definition of reduced pressure, temperature, and volume given above:

$$\phi = \frac{v}{\phi_0}, \quad \pi = \frac{p}{\pi_0}, \quad \text{and} \quad \theta = \frac{T}{\theta_0}.$$

Therefore:

$$\left(\pi + \frac{3}{\phi^2}\right)\left(3\phi - 1\right) = 8\theta \cdot$$

We have now eliminated the constants, a and b, which depend upon the particular compound used, and have obtained a general equation of state, in which p, v, and T are represented as fractions of the absolute critical values. ϕ is a function of π and θ and it is the same function for all substances.

The change of volume $\phi_2 - \phi_1$, produced in the liquid by an elevation of temperature from θ_2 to θ_1 at constant pressure, π, is therefore:

$$\phi_2 - \phi_1 = f(\pi, \theta_2) - f(\pi, \theta_1).$$

Dividing by $\phi_1 = f(\pi, \theta_1)$,

$$\frac{\phi_2 - \phi_1}{\phi_1} = \frac{f(\pi, \theta_2) - f(\pi, \theta_1)}{f(\pi, \theta_1)},$$

and since $\phi = \frac{v}{\phi_0}$:

$$\frac{v_2 - v_1}{v_1} = \frac{f(\pi, \theta_2) - f(\pi, \theta_1)}{f(\pi, \theta_1)}.$$

Now, v_1 and v_2 are the ordinary specific volumes of the substance under investigation, at two temperatures, θ_1 and θ_2.

In other words, the equation states that all liquids and gases expand the same fraction of their original volumes, when heated from one corresponding temperature to another at constant pressure. Hence, if we know the coefficient of expansion of one liquid over a long range of temperature, and we know also its critical temperature, we may calculate the expansion of any other liquid whose critical temperature is also known. The following data have been supplied by Young and Ramsay.*

Substance	Mol. Wt.	θ_0 T. Abs.	π_0 M.M. Hg.	ϕ_0 C.C. per G.
Methyl alcohol	31.93	513.0	59,760	3.697
Ethyl alcohol	45.90	516.1	47,850	3.636
Propyl alcohol	59.87	536.7	38,120	3.634
Acetic acid	59.86	594.6	43,400	2.846
Ether	73.84	467.4	27,060	3.801
Benzene	77.84	561.5	36,395	3.293
Fluorbenzene	95.80	559.5	33,912	2.822
Chlorbenzene	112.2	633.0	33,912	2.731
Brombenzene	156.6	670.0	33,912	2.059
Iodobenzene	203.4	721.0	33,912	1.713
Carbon tetrachloride	153.5	556.2	34,180	1.799

FLUORBENZENE

Temperature	Vapor Pressure	Molecular Volume	Temperature	Vapor Pressure	Molecular Volume
272.3	20	91.47	410.4	3000	110.03
289.3	50	93.20	423.8	4000	112.64
303.9	100	94.92	434.8	5000	114.98
320.2	200	96.80	444.2	6000	117.06
338.7	400	99.05	452.8	7000	119.14
358.1	760	101.59	460.4	8000	121.19
367.3	1000	102.90	473.6	10000	125.04
382.0	1500	105.10	484.9	12000	128.80
393.2	2000	107.00	499.7	15000	134.64

The density of ether at 10° C. is 0.7249. Let us use the data given in the tables to calculate its density at 46°. We have:

$$\theta_1 = \frac{273 + 10}{467.4} = 0.6055,$$

$$\theta_2 = \frac{273 + 46}{467.4} = 0.6827.$$

* *Phil. Mag.* (5) **33**, 153 (1892); *ibid.* (5) **34**, 505 (1892).

For fluorbenzene

$$\theta_0 = 559.5°$$
$$\theta_1 = 559.5 \times 0.6055 = 339°$$
$$\theta_2 = 559.5 \times 0.6827 = 382°$$

At these temperatures the molecular volumes of fluorbenzene are 99.05 and 105.10, respectively. The specific volumes are, therefore:

$$\frac{99.05}{95.8} = 1.0339 \quad \text{and} \quad \frac{105.10}{95.8} = 1.0960$$

and

$$\frac{1.0960 - 1.0339}{1.0339} = \frac{0.0631}{1.0339} = 0.0610$$

The density of ether at 10° was given as 0.7249, corresponding to a specific volume of 1.3794. Its specific volume, v_2, at 46°, is given by the equation:

$$\frac{v_2 - 1.3794}{1.3794} = 0.0610$$

or

$$v_2 = 1.3794 \times 1.0610 = 1.4635,$$

and its density is:

$$\frac{1}{1.4635} = 0.6901.$$

There are many other applications of the principle of corresponding states. According to Trouton's rule, the molal heat of vaporization, L, divided by the absolute temperature used in the process of converting the liquid into vapor, is the same for all substances $\left(\frac{L}{T} = K\right)$. But this is only approximately true. Nernst observed that the ratio increases with the temperature, and proposed a formula in which the entropy of vaporization is represented, not as a constant quantity, but as a function of the temperature:

$$\frac{L}{T} = 9.5 \log T - 0.007\ T.$$

Even this formula fails at very high temperatures and Forcrand* sought to extend its range of usefulness by introducing other arbitrary constants. His formula is:

$$\frac{L}{T} = 10.1 \log T - 1.5 - 0.009\ T - 0.0000026\ T.$$

* Forcrand, *Compt. rend.*, **156**, 1439, 1448 (1913).

Now, the simple expression of Trouton's rule applies to all normal (unassociated and undissociated) liquids, if, instead of comparing the molal heats of vaporization under one atmosphere, or under any other arbitrarily chosen pressure, we make the comparisons at temperatures which produce equal vapor pressures.* That is to say, the entropy change due to passage from the liquid to the vapor state is the same for all liquids, if measured at temperatures that produce equal concentrations of molecules in the vapor phases.

* Hildebrand, *J. Am. Chem. Soc.*, **37**, 970 (1915).

APPENDIX

Formulas

From analytical data the simplest empirical formula of a compound may be calculated. The relative weights of the elements found in a compound divided by their respective atomic weights must give the numerical ratios in which the atoms of the different elements exist in the molecule. A substance, for example, has the composition: carbon, 40 per cent; hydrogen, 6.6 per cent; oxygen, 53.3 per cent. The atoms of carbon, hydrogen, and oxygen in the molecule must be associated in the ratio $\frac{40.0}{12} : \frac{6.6}{1} : \frac{53.3}{16}$ or 3.3 to 6.6 to 3.3. Since, from the law of multiple proportion, we conclude that molecules do not contain fractional parts of atoms we must express these ratios in whole numbers. The smallest whole numbers representing these relative values are 1 : 2 : 1 and hence the simplest empirical formula for the compound is CH_2O. The same ratios are expressed, however, by the formulas $C_2H_4O_2$, $C_3H_6O_3$, $C_6H_{12}O_6$, or, in general, $C_nH_{2n}O_n$. All of these formulas correspond to the composition indicated above. In order to determine which formula should be assigned to the substance under investigation we must know its molecular weight. Formaldehyde (mol. wt. 30) has the formula CH_2O. Acetic acid (mol. wt. 60) has the formula $C_2H_4O_2$. Lactic acid is $C_3H_6O_3$ and glucose is $C_6H_{12}O_6$. The best methods for estimating molecular weights are based upon the gas laws and upon principles relating to the properties of solutions.

Molecular Weights from Properties of Gases

Vapor density methods are usually employed in determining the molecular weights of all compounds that vaporize without decomposition. According to Avagadro's law, equal volumes of all gases at the same temperature and pressure contain the same number of molecules. In other words the molecular weights of all gases under identical conditions of temperature and pressure occupy the same volume. At 0°C. and 760 mm. pressure the gram molecular volume is 22.4 liters. The molecular weight of a substance is, therefore, the weight of 22.4 liters of its vapor under standard conditions.

A convenient formula for calculating molecular weights may be derived from the gas laws as follows:

Begin with one mol of gas occupying volume v at pressure p and temperature T. Suppose the pressure is changed from p to p'; the volume will change to some new value V. From Boyle's law

$$pv = p'V \quad \text{and} \quad V = \frac{pv}{p'}. \tag{1}$$

Now, keeping the pressure constant at p', let the temperature be changed to T'. The volume will again be changed; this time from V to v'; and from Charles's law

$$\frac{V}{T} = \frac{v'}{T'} \quad \text{or} \quad V = \frac{v'T}{T'}; \tag{2}$$

equating the equal values of V in (1) and (2) we have

$$\frac{pv}{p'} = \frac{v'T}{T'}. \tag{3}$$

Multiplying both sides of this equation by p' and dividing by T we obtain the equation

$$\frac{pv}{T} = \frac{p'v'}{T'}. \tag{4}$$

That is to say, the value of $\frac{pv}{T}$ is a constant quantity. The gas constant is usually represented by R and the equation is written

$$\frac{pv}{T} = R \quad \text{or} \quad pv = RT. \tag{5}$$

Substituting for T the absolute temperature, for p the pressure in atmospheres, and for v the volume in liters occupied by a mol of gas under these conditions, we obtain the numerical value 0.082 for the constant R.*

To make the equation general, an additional factor must be introduced, namely, n, the number of mols or the fractional part of a mol measured. The expression then becomes

$$pv = nRT. \tag{6}$$

* The numerical value of the gas constant, R, depends upon the units employed in pressure and volume measurements.

P	V	R
atmospheres	liters	0.0821
atmospheres	cc.	82.1
mm. Hg.	cc.	62360
dynes/cm.^{2}	cc.	8.31×10^7

One calorie is equivalent to 4.18×10^7 ergs; hence in units of heat capacity $R = \frac{8.31}{4.18} = 1.99$ cals. or, approximately, 2.

We may substitute for n the ratio $\frac{W}{M}$ in which W is the weight of the gas measured and M its molecular weight.

Then $$pv=\frac{WRT}{M} \quad \text{or} \quad M=\frac{WRT}{pv}. \tag{7}$$

Many practical methods for determining the values required in this equation have been devised. In dealing with the permanent gases it is only necessary to weigh an evacuated flask of known volume and weigh again after filling it with the gas at atmospheric pressure and room temperature. For volatile liquids the Victor Meyer method is convenient but lacks precision. A weighed sample of the liquid under investigation is sealed in a small glass bulb, G (Fig. 1), which rests on a rod, E, in the upper end of a long glass tube, A. An air-tight rubber connection is made between the rod E and the side arm of the tube. The tube A is heated to a temperature above the boiling point of the sample in G by the vapor of a liquid which is kept boiling in the outer jacket B. After the tube A has acquired the temperature of the vapor bath surrounding it, an air-tight stopper is inserted in the top of tube A, then the sample is dropped from the detent by pulling out on the rod E. The rubber connection stretches enough to let the bulb fall. On striking the bottom of A the capillary end of the bulb is broken and the sample immediately vaporizes forcing an equivalent volume of air into the eudiometer D, which at the beginning of the experiment is filled with water. Since all gases have practically the same coefficient of expansion the volume of air received by the eudiometer represents the volume that the weighed sample would occupy if it could exist as a vapor at the temperature of the room under atmospheric pressure. The variables P, W, and T are fixed in advance by the conditions of the experiment and V is measured.

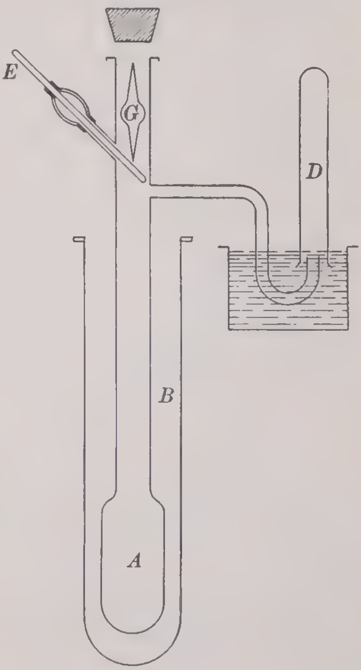


FIG. 1

According to the method of Chapin a weighed sample is evaporated in an apparatus of known volume and the change in pressure is measured.[1]

The temperature, T, is the variable measured in the method[2] represented in Fig. 2. The volume of the glass bulb A from the capillary at C to the point marked E is accurately determined. Platinum wires are sealed into the stem of the bulb at E and F. These wires are connected with the poles of a battery, B, through the relay R. Mercury is poured into the reservoir G until the surface of the mercury makes contact with the platinum point at E. A small thin walled glass bulb containing a weighed sample of the liquid is introduced into A. A short glass tube with one end ground to fit the neck of the flask and the other end drawn out to a capillary is connected by means of heavy rubber tubing to the upper end of A. By means of compressed air mercury is forced from the reservoir into A until it rises to the top of the capillary at C. The end of the capillary is then sealed. The oil bath surrounding A is heated by means of an electric current passing through coils of nichrom wire. The current is turned on and off automatically through the operation of the relay R. The capillary end of the sample tube is broken off by bending the rubber joint at D and the sample is thereby released on the surface of the mercury. As the specimen vaporizes mercury is forced back into the reservoir. The temperature of the bath is raised until the vapor fills the bulb to the point E. The break in contact between the mercury and the platinum point is indicated by the relay, and at the same time the current is turned off from the heating coils, H, in the oil bath. Due to a lag in the temperature of the vapor, the mercury level continues to fall for a short time after the heat is turned off; but as the oil bath cools the mercury rises. When contact with the platinum is made again the heat is turned on automatically, and within fifteen or twenty minutes the "make and break" of contact correspond to changes of only one or two tenths of a degree

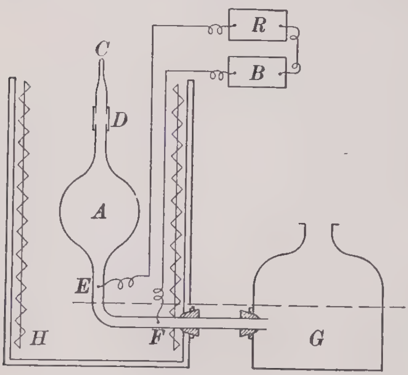


FIG. 2

[1] Chapin, *J. Phys. Chem.*, **22**, 337 (1918).
[2] Porter, *J. Am. Chem. Soc.*, **34**, 1290 (1912).

in the temperature of the oil bath. The mercury now stands at the same level in both sides of the apparatus, and the temperature at which the known weight of substance fills a given volume at atmospheric pressure is observed.

Molecular Weights from Properties of Solutions

Many compounds decompose when heated and cannot be obtained in the vapor state. Methods based upon the gas law cannot be used in such cases. Raoult's discovery that the lowering of the vapor pressure of a solvent by a dissolved substance is determined by the relative number of molecules of solute and of solvent in any solution, and is independent of the mass of the dissolved molecule, gives a means of estimating the molecular weight of a dissolved substance by vapor pressure measurement or by the measurement of any definite function of the change in vapor pressure such as osmotic pressure, freezing point lowering, or elevation of boiling point.

VAPOR PRESSURE

The vapor pressure of pure water at 20° is sufficient to support a column of mercury 17.36 mm. high. In a solution containing one mol of sugar and seventy mols of water the mol fraction of water is 70/71 and the vapor pressure of the solution at 20° is

$$70/71 \times 17.36 = 17.11 \text{ mm.}$$

The vapor pressure of the solvent is proportional to its mol fraction in the solution. The lowering of the vapor pressure (in this case 1/71 of the original value) is proportional to the mol fraction of the solute. In general terms Raoult's law is written $\frac{p_0 - p}{p_0} = \frac{n}{N+n}$ where p_0 and p are the vapor pressures of the pure solvent and of the solution respectively, N is the number of mols of the solvent, and n is the number of mols of the solute. Or $p = p_0X_0$ if X_0 is the mol fraction of the solvent in the solution. In the pure solvent $X_0 = 1$.

In very dilute solutions $n + N$ does not differ appreciably from N; and, representing $p_0 - p$ by the symbol Δp, we have

$$\frac{\Delta p}{p_0} = \frac{n}{N}.$$

BOILING POINT AND FREEZING POINT

The curve BC (Fig. 3) represents the vapor pressure of a pure liquid between its freezing point and boiling point. The vapor pressure of the solid phase is indicated by AB. The curve DE represents the vapor pressure of a solution. As the temperature rises the

vapor pressure of the pure solvent or of any solution increases until it reaches a value equal to atmospheric pressure. The liquid then boils at constant temperature. Boiling point may be defined as the temperature at which the vapor pressure of the liquid is equal to the pressure of the atmosphere resting upon its surface. The freezing point is the temperature at which the liquid and solid phases have the same vapor pressure. Since the vapor pressure of a solvent is lowered by dissolved molecules, the boiling point of a solution must be higher and the freezing point lower than the corresponding points for the pure solvent. The elevation of the boiling point or depression of the freezing point is represented by the symbol Δt.

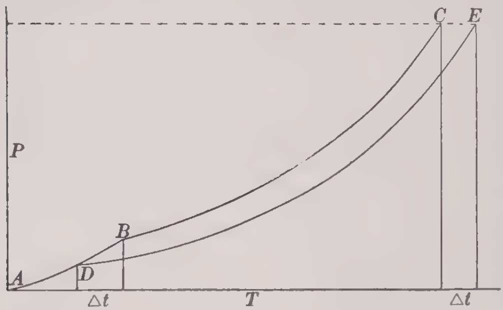


Fig. 3

When one mol of any substance, which does not dissociate nor associate in solution, is dissolved in 1000 grams of water the freezing point is lowered 1.86° and the boiling point is elevated 0.52°. For any quantity of solute in 1000 grams of water $\Delta t = 1.86 \times \frac{W}{M}$, if W is the weight of dissolved substance and M its molecular weight. Representing the weight of water used by G, an additional factor, $\frac{1000}{G}$, may be introduced to indicate the effect of changing the concentration of the solution by varying the amount of solvent used.

Then
$$\Delta t = 1.86 \times \frac{W}{M} \times \frac{1000}{G}.$$

Substituting K for the product of the two constants,

$$M = \frac{KW}{G\Delta t}:$$

Values of K for Various Solvents

Solvent	F. P. Const.	B. P. Const.
Water	1863	520
Acetic acid	3860	260
Benzene	5000	328
Ether	—	300

It will be observed that K is the theoretical value of Δt for a solution containing one mol of solute per gram of solvent. K may be calculated from the molal heat of vaporization, L, and the absolute temperature, T, at which the solvent is vaporized, or from the heat of fusion, L, and the temperature, T, at which the pure solvent melts:

$$K = \frac{RT^2}{L}.$$

Thus for water,

$$K_B = \frac{2 \times (373)^2}{537} = 520,$$

and

$$K_F = \frac{2 \times (273)^2}{80} = 1863.$$

A definite relationship existing between changes in boiling point and molal concentration of a solution is expressed in the equation

$$\Delta t = \frac{RT^2}{L} \cdot \frac{n}{N+n},$$

or

$$\Delta t = kx.$$

In this equation L is the heat of vaporization or heat of fusion of one mol (not one gram) of the solvent; hence k is equal to K (page 468) divided by the molecular weight of the solvent, and x is the mol fraction of the solute.

Values of k for Various Solvents

Solvent	F. P. Const.	B. P. Const.
Water	104	29
Acetic acid	64.3	4.3
Benzene	64.1	4.2
Ether	—	4.1

OSMOTIC PRESSURE

The osmotic pressure of a solution is definitely related to the lowering of the vapor pressure caused by the dissolved substance. Therefore, the mol fraction of a solute and its molecular weight may be determined from osmotic pressure measurements.

If in an inclosed space (Fig. 4) a solution, l, be separated from the pure solvent, s, by means of a semi-permeable membrane, m, pure solvent will pass through the membrane in one direction or the other until equilibrium is reached, that is, until the solution has such concentration that its osmotic pressure is exactly equal to the weight of the column of solvent supported. Let the height of this column be h. Now, the vapor pressure of the solution, l, must be

exactly equal to the pressure of the vapor of the pure solvent in the saturated atmosphere at the same level; that is, at the distance h above the surface of the solvent. Any inequality in these values would result in perpetual motion, the solvent continually moving through the membrane in one direction with a corresponding movement of the vapor in the opposite way. The difference between the vapor pressure of the solvent and solution corresponds, therefore, to the difference between the pressures of the vapor of the solvent at the levels of the two liquid surfaces h cm. apart. The change in pressure, dp, corresponding to a small change in elevation above the surface of the solvent is determined by the density, D, of the vapor in that region and the magnitude of the change in altitude, dh:

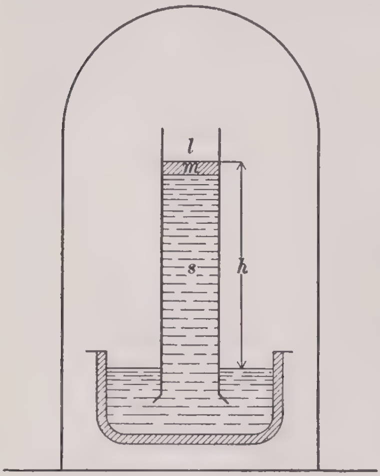


FIG. 4

$$dp = Ddh. \tag{1}$$

From the gas laws we have $pv = \dfrac{WRT}{M}$ (p. 465); (2)

then $$p = \frac{W}{v} \cdot \frac{RT}{M} \quad \text{and} \quad \frac{W}{v} = \frac{Mp}{RT}. \tag{3}$$

But $$\frac{W}{v} = D, \text{ the density of the vapor;}$$

hence $$p = \frac{RTD}{M} \quad \text{and} \quad D = \frac{Mp}{RT}. \tag{4}$$

Substituting this value of D in (1),

$$dp = \frac{Mp}{RT} dh \quad \text{or} \quad \frac{dp}{p} = \frac{M}{RT} dh. \tag{5}$$

Integrating between the values of p_0 and p, the vapor pressures of the solvent and solution respectively,

$$\log \frac{p_0}{p} = \frac{Mh}{RT} \quad \text{or} \quad h = \frac{RT}{M} \log \frac{p_0}{p}. \tag{6}*$$

We now have the height of the column of solvent in terms of the molecular weight, M, of the solvent, the temperature, T, and the

* Natural logarithms.

vapor pressures of solvent and solution. The osmotic pressure, P_{os}, is equal to the height of the column, h, multiplied by the density, D_0, of the solvent.

$$P_{os}=hD_0.$$

Then
$$P_{os}=\frac{RTD_0}{M}\log\frac{p_0}{p}. \tag{7}$$

This equation is quite exact over any range of concentration if the vapor of the solvent obeys the gas law.

According to Raoult's law,

$$\log\frac{p_0}{p}=\log\frac{N+n}{N}=\log\left(\frac{n}{N}+1\right).$$

Expanding this into a powers series,

$$\log\left(\frac{n}{N}+1\right)=\frac{n}{N}-\frac{1}{2}\left(\frac{n}{N}\right)^2+\frac{1}{3}\left(\frac{n}{N}\right)^3\cdots.$$

In dilute solutions $\frac{n}{N}$ is a small fraction and the higher powers of the fraction become negligible. Assuming that all terms except the first may be neglected for dilute solutions, we have

$$P_{os}=\frac{RTD_0}{M}\cdot\frac{n}{N}.$$

The product, MN, is the weight of the solvent (mol. wt. times the number of mols) and D_0 is its density,

therefore
$$\frac{D_0}{MN}=\frac{1}{V_0}$$

and
$$P_{os}=\frac{nRT}{V_0}, \tag{8}$$

where V_0 is the volume of the pure solvent. This is the well-known Morse and Fraser equation. By making one more approximation, namely, that the solvent and solution have the same density, which is true only at infinite dilution, we obtain the van't Hoff equation,

$$P_{os}=\frac{nRT}{V}, \tag{9}$$

in which V is the volume of the solution.

Van't Hoff developed the equation in an empirical way from observations leading to the conclusion that dissolved substances obey the gas laws. It is true that the osmotic pressure of a dilute solution varies as the absolute temperature (Charles' law) and is proportional to the number of mols of solute per unit volume (Boyle's law), but the nature of osmotic pressure is totally different from that of an effect produced by the bombardment of the walls of a vessel by gas molecules.

It must be remembered that the methods given above for molecular-weight determinations are based upon the assumption that the vapors obey the gas laws, and that solutions act in accord with Raoult's law. In actual experience a perfect gas is never found; and a solution that shows no deviations from the laws of perfect solutions is never encountered. Hence, molecular-weight determinations are inexact. In most cases, however, such determinations are used as a basis for deciding whether a compound should be represented by its simplest empirical formula or some multiple of this value. The methods are good enough to serve this purpose.

QUESTIONS AND PROBLEMS FOR REVIEW

1. A mixture of hydrogen, nitrogen, and methane was exploded with a measured volume of oxygen. The residual gas was shaken with a saturated solution of potassium hydroxide. All gas measurements were made under atmospheric pressure and at a constant temperature. From the following data calculate the percentages, by volume, of the three gases in the original mixture:

Volume of mixed gases	40 cc.
Volume of oxygen added	80 cc.
Volume after explosion	56 cc.
Volume after absorption by KOH . .	36 cc.

2. A compound has the following composition: $C = 62.05$ per cent, $H = 10.35$ per cent, $O = 27.60$ per cent. At 20° and 760 mm. 1.12 liters of its vapor weighs 2.7 grams. Write the formula of the compound.

3. Devise a means of estimating the quantity of each gas present in a mixture of methane, nitrogen, and carbon dioxide.

4. The formula of ethane is C_2H_6. Calculate the weight of a liter of the gas at 30° and 700 mm.

5. Calculate the density of a mixture of equal volumes of pentane vapor and air at 90° C. and 760 mm.

6. Write a graphic formula for each of three compounds having the formula C_4H_8, and devise a method for making each.

7. What volume of air is required to burn one liter of ethane? What volume of carbon dioxide would be formed?

8. A mixture of oxygen and ethane at 20° measured 110 cc. The mixture was exploded by means of an electric spark. After the products had cooled to room temperature the volume was 60 cc. After treatment with potassium hydroxide solution the residual gas, which was oxygen, occupied 20 cc. Find the per cent of ethane in the original mixture.

9. Write equations representing two methods for making ethylene and two methods for making acetylene.

10. A substance was analyzed by the combustion method. Calculate its percentage of carbon and hydrogen from the following data:

Weight of sample	0.2046 gram
Weight of water formed	0.1255 gram
Weight of carbon dioxide	0.2985 gram

11. A sample weighing 0.508 gram was analyzed by the Kjeldahl method. The ammonia produced was collected in 50 cc. of normal sulphuric acid. The residual acid was then neutralized by 45 cc. of normal potassium hydroxide. Calculate the percentage of nitrogen in the sample.

12. One gram of a substance was dissolved in 30 grams of water. The freezing point of the solution was found to be − 0.101°. Find the molecular weight of the solute.

13. A hydrocarbon was analyzed with the following results: weight of sample, 0.280 gram; weight of CO_2 produced, 0.880 gram; weight of H_2O formed, 0.360 gram. The vapor density of the compound was measured by the Victor Meyer method. A sample weighing 0.1470 gram displaced 43.2 cc. of air measured at 20° and 740 mm. Write its molecular formula.

✓14. Write structural formulas for the products formed when ethylene reacts (*a*) with Br_2, (*b*) with H_2SO_4, (*c*) with HI, (*d*) with HOCl.

15. How would you estimate the quantity of ethane, ethylene, and acetylene in a mixture of the three gases?

16. Outline an analytical procedure for determining the composition of a mixture of oxygen, methane, and ethylene.

17. How would you detect the presence of unsaturated hydrocarbons in kerosene?

18. How would you distinguish between allene ($CH_2{=}C{=}CH_2$) and allylene ($CH_3{-}C{\equiv}CH$)?

19. Outline methods for detecting the presence of carbon and hydrogen in organic compounds. Explain the tests.

20. Outline qualitative tests for sulphur and nitrogen in organic compounds. How are the same elements estimated quantitatively?

21. Write the structural formulas of the hexanes, and name them.

22. Calculate the volume of 15 grams of ethane at 40° and 640 mm. Calculate the weight of a liter of methane under standard conditions.

23. Calculate the heats of formation (*a*) of propane, (*b*) of propylene, (*c*) of acetylene (see p. 42).

24. Calculate the percentage composition of each of the following compounds: (*a*) $C_6H_5NH_2$, (*b*) C_2H_5CN, (*c*) CHI_3.

25. How would you estimate the quantity of alcohol in a mixture of ethyl alcohol and hexane?

26. Write equations representing three general reactions of alcohols.

27. A saturated compound having the formula $C_3H_8O_3$ is converted by acetyl chloride into one having the formula $C_9H_{14}O_6$. Write a structural formula for each of these compounds.

✓28. Outline a method for making (*a*) ethyl alcohol from methyl alcohol; (*b*) methyl alcohol from ethyl alcohol.

✓29. Devise methods for making the following compounds from ethyl alcohol: (*a*) $CH_3 \cdot COOH$, (*b*) $CH_3 \cdot CH_2Cl$, (*c*) $(CH_3CO)_2O$, (*d*) $CH_2{=}CH_2$, (*e*) $CH_2Br \cdot CH_2Br$.

✓30. Beginning with methyl alcohol and any necessary reagents, show how the following compounds may be prepared: (*a*) C_2H_6, (*b*) C_2H_4, (*c*) C_2H_2, (*d*) $CH_3CH : CH_2$.

31. Write the structural formulas of the hexyl alcohols, and name each.

32. Write balanced equations representing the action of the following reagents upon ethyl alcohol: (*a*) H_2SO_4, (*b*) CH_3COOH, (*c*) PCl_3, (*d*) $K_2Cr_2O_7 + H_2SO_4$.

33. Show how propylene glycol ($CH_3—CHOH—CH_2OH$) may be made from propyl alcohol.

34. How would you accomplish the complete removal of water and alcohol from ether?

35. A mixture of alcohol and concentrated H_2SO_4 contains ethyl sulphuric acid. How could you employ this mixture to prepare ethylene? ether? How do the experimental conditions differ in the two cases? Write equations for both processes.

36. Discuss the preparation and the properties of diethyl ether.

37. A sample of ether weighing 0.667 gram was vaporized and heated until the vapor occupied 300 cc. under 680 mm. The temperature required was 90°. Find the molecular weight of ether.

38. How would you prepare ethylene from the following compounds: $CH_3 \cdot CH_2OH$? $CH_3 \cdot CH_2I$? $CH_2Br \cdot CH_2Br$? How would you prepare each of these compounds from ethylene?

39. Calculate the weight of ethyl bromide that may be prepared from 20 grams of alcohol through the agency of phosphorus tribromide.

40. Account for the following facts:

(*a*) Several substances have the formula C_4H_{10}.
(*b*) One substance only has the formula CH_2Cl_2.
(*c*) Two substances have the formula $CH_3CH{=}CH—CO_2H$.
(*d*) AgI is not precipitated when $AgNO_3$ solution is added to CH_3I.

41. Two compounds having the formula $C_2H_4Cl_2$ are known. Write their structural formulas and show how they may be made.

42. Two compounds have the formula $C_2H_5NO_2$. On reduction one yields an alcohol and the other an amine. Assign to each a graphic formula.

43. Write equations representing the conversion of alcohol into chloroform.

44. Two compounds have the formula C_3H_9N. Nitrous acid converts one of them into C_3H_8O, and the other into $C_3H_8N_2O$. Write a graphic formula for each of the four compounds.

45. Give two methods for separating primary, secondary, and tertiary amines.

46. Outline two methods for making pure primary aliphatic amines.

47. Beginning with normal propyl alcohol and any necessary reagents, outline methods for making (*a*) isopropyl alcohol, (*b*) ethylamine.

48. Specify the reagents and the experimental conditions required to make the following conversions:

CH_3NH_2 to CH_3OH,	CH_4 to CH_3COOH,
CH_3OH to CH_3Br,	CH_3COOH to CH_4,
$CH_2{=}CH_2$ to CH_3CH_2I,	CH_3CH_2I to $CH_2{=}CH_2$,
$CH_3CH_2CH_2OH$ to $CH_3CHOHCH_3$,	CH_3CONH_2 to CH_3NH_2.

49. Outline chemical tests that may be used to distinguish between the members of the following pairs of compounds:

(*a*) $C_2H_5NH_2$ and $CH_3—CO—NH_2$,
(*b*) $(C_2H_5)_2O$ and $C_2H_5—CO—OC_2H_5$,
(*c*) $(CH_3)_2O$ and $CH_3—CH_2OH$,
(*d*) $CH_3—CO—CH_3$ and $CH_3—CH_2OH$,
(*e*) C_2H_5Cl and $CH_3—COCl$,
(*f*) $CH_3—CH_2—CHO$ and $CH_3—CO—CH_3$,
(*g*) $CH \equiv C—C_2H_5$ and $CH_3—C \equiv C—CH_3$.

50. Write five possible structures for compounds having the formula $C_4H_8O_2$. Outline chemical reactions that may be used to identify each compound.

51. Outline two methods for separating ethyl alcohol and acetone without distilling the mixture.

52. Acetone, acetic acid, and methyl alcohol are present in an aqueous solution. How would you separate the components and obtain each in a pure state?

53. How would you separate methyl alcohol and acetone (boiling points 66° and 56.3°)?

54. How would you distinguish between acetaldehyde and acetone in dilute aqueous solution?

55. By what chemical tests could you distinguish between *n*-propyl alcohol, *iso*-propyl alcohol, and acetone?

56. Write equations representing five general reactions of aldehydes.

57. What reactions can be used for the quantitative determination of aldehydes?

58. If given a pure substance, how would you determine by chemical means whether it is:

(*a*) $CH_3—\overset{\overset{\displaystyle O}{\|}}{C}—O—C_2H_5$ or $C_2H_5—\overset{\overset{\displaystyle O}{\|}}{C}—O—CH_3$?
(*b*) $CH_3—CO—CH_3$ or $CH_3—CH_2—CHO$?
(*c*) $CH_3—O—CH_3$ or $CH_3—CH_2OH$?
(*d*) $C_6H_4\left\langle\begin{matrix} OH \\ CH_3 \end{matrix}\right.$ or $C_6H_5—CH_2OH$?

59. Beginning with acetone and any necessary reagents, show how the following compounds may be made: (*a*) $(CH_3)_3COH$, (*b*) $(CH_3)_2CCl_2$, (*c*) $(CH_3)_2CHOH$, (*d*) $(CH_3)_2C : CH_2$.

60. Write four possible structures for compounds having the formula C_3H_7NO. Outline chemical reactions that may be used to identify each compound.

61. Write all possible structures for a compound having the formula C_3H_8O. Describe one compound having this formula and outline an experimental procedure that could be used to determine which structure should be assigned to it.

62. Indicate chemical reactions that may be used to distinguish between

(*a*) $CH_2{=}CH_2$ and $CH_3{-}CH_3$,
(*b*) $CH_3{-}CH_2OH$ and $CH_3{-}O{-}CH_3$,
(*c*) $CH_3{-}CH_2CN$ and $CH_3{-}CH_2{-}CH_2NH_2$,
(*d*) $CH_3{-}CHOH{-}CH_3$ and $CH_3{-}CH_2{-}CHO$,
(*e*) $CH_3{-}CH_2{-}CHO$ and $CH_3{-}CO{-}CH_3$,
(*f*) $CH_3{-}CH_2{-}NH_2$ and $CH_3{-}NH{-}CH_3$.

63. Write equations representing methods for preparing each of the following classes of compounds: amines, alcohols, aldehydes, ketones, alkyl halides.

64. Two compounds each having the formula C_3H_8O were oxidized. One of them was converted into C_3H_6O and the other yielded $C_3H_6O_2$. Neither of these products could be further oxidized without loss of carbon. Write the structural formulas of the original compounds.

65. Write equations for the conversion of $CH_3{-}CH_2{-}CH_2{-}COOH$ (*a*) into $CH_3{-}CH_2{-}CHBr{-}COOH$, (*b*) into $CH_3{-}CHBr{-}CH_2{-}COOH$, (*c*) into $CH_3{-}CH{=}CH{-}COOH$.

66. A compound having the formula $C_2H_2Br_2O$ was converted by cold water into $C_2H_3BrO_2$. Write structural formulas for the two compounds.

67. A solution of 0.60 gram of acetic acid in 50 grams of water freezes at − 0.376°. A solution of 1.16 grams of acetic acid in 50 grams of benzene freezes at 4.43°. At 87° and 760 mm. 4 grams of acetic acid vapor occupy a volume of 1968 cc. Calculate the molecular weight of the acid from each set of data. Interpret the results.

68. Write a balanced equation for the oxidation of $C_6H_5{-}CHO$ to $C_6H_5{-}COOH$ with $Na_2Cr_2O_7$ in aqueous acid solution.

69. Show how acetic acid, acetic anhydride, and acetamide may be made from acetyl chloride.

70. Indicate by means of balanced equations the action of propionyl chloride (*a*) on water, (*b*) on ammonia, (*c*) on ethyl alcohol, (*d*) on sodium propionate.

71. State how many liters of oxygen measured under standard conditions would be required to burn one mol of each of the following substances to CO_2 and H_2O: (*a*) CH_4, (*b*) CH_2O, (*c*) C_2H_5OH, (*d*) CH_3CO_2H.

72. Devise methods for converting normal propyl alcohol (*a*) into ethane, (*b*) into acetylene, (*c*) into *iso*-butyric acid.

73. Why is phenolphthalein and not methyl orange used as an indicator in titrating organic acids?

74. On the destructive distillation of sodium propionate with soda lime, a combustible gas was obtained which decolorized bromine only in the sunlight. It had a density 1.03 times as great as air. Does the molecular weight agree with that of the compound you would expect to get by this process?

75. Account for the fact that formic acid is the only member of the fatty acid series that acts as a reducing agent.

76. Write graphic formulas for the acids having the formula $C_5H_{11}COOH$. Name each.

77. How many equivalents of an oxidizing agent does it take to oxidize one mol of a primary alcohol to an aldehyde? to an acid? How many grams of $KMnO_4$ in alkaline solution would be required to convert one mol of ethyl alcohol to potassium acetate?

78. How would you proceed to make an α-brom derivative of a saturated monobasic acid? How would you make a β-brom derivative of the same acid?

79. In the preparation of ethyl acetate from alcohol and acetic acid how will the yield be affected by the addition of sulphuric acid? of water? of methyl alcohol? Give reasons for your replies.

80. Show by means of formulas how α-hydroxy, β-hydroxy, and γ-hydroxy acids behave when heated.

81. Sixty grams of acetic acid with 46 grams of ethyl alcohol gave an equilibrium mixture containing 58.7 grams of ethyl acetate; calculate the equilibrium constant. One mol of acetic acid is mixed with three mols of alcohol; calculate the maximum yield of ester (no dehydrating agent present).

82. How does PCl_5 act upon water? upon alcohol? upon an ester? upon a ketone?

83. Explain the functions of sulphuric acid in the manufacture of ether, ethylene, and ethyl acetate when methods are employed that involve the use of ethyl alcohol.

84. Calculate the weight of iodine that will be decolorized by five grams of dioleostearin.

85. Two esters have the formula $C_4H_8O_2$. Write their structural formulas and tell how each can be identified.

86. One mol of an ester is shaken with one mol of water until no further change occurs. What products are present in the mixture thus produced? How would the relative amounts of each product be changed by the addition (*a*) of anhydrous calcium chloride? (*b*) of sodium hydroxide?

87. If a substance were known to be either an alcohol, an aldehyde, or an ester, what tests would you use to identify the class to which it belongs?

88. Starting with ethyl acetate and inorganic reagents, how could you obtain ethyl iodide?

89. A compound, on hydrolysis, gives *iso*-propyl alcohol and normal butyric acid. Write the structural formula of the compound.

90. How could you distinguish between an amide and an amine? a nitro compound and a nitrite? an aldehyde and a ketone? an alkyl halide and an acyl halide?

91. How do fats differ from waxes?

92. A fat consists of stearin 80 per cent, palmitin 12 per cent, olein 5 per cent, linolein 3 per cent. Calculate its iodine number.

93. An oil contains 4 per cent of linolein. The other components are olein, stearin, and palmitin. Its iodine value is 85. Find the per cent of olein in the oil.

94. How could you convert an acid into an acid chloride? an acid chloride into an ester? a nitro compound into an amine? an amine into an alcohol or phenol?

95. Outline methods for replacing (*a*) Br by CN, (*b*) NH_2 by OH, (*c*) COOH by H, (*d*) H by COOH, (*e*) CH_2OH by CHO, (*f*) CO by CROH, (*g*) CO by CNOH.

96. Show how bromine may be substituted for the underlined atoms or groups in the following: (*a*) $C_2H_5\underline{OH}$, (*b*) $(CH_3)_2C\underline{O}$, (*c*) $CH_3CONH\underline{H}$, (*d*) $(CH_3)_4N\underline{OH}$.

97. Express by equations or in words how you would obtain an alcohol from an alkyl halide, an acid from an alcohol, an ester from an acid, an acid amide from an ester.

98. How would you distinguish between ethyl nitrite and nitroethane? between ethyl acetate and methyl propionate?

99. How could ethyl alcohol be made from (*a*) $C_2H_5NH_2$, (*b*) $C_2H_5CONH_2$, (*c*) C_2H_5I?

100. How could ethylamine be made from (*a*) C_2H_5OH, (*b*) $C_2H_5CONH_2$, (*c*) C_2H_5I?

101. Indicate by means of equations any reactions that might take place between (1) C_2H_5Br, (2) C_6H_5Br, or (3) CH_3COBr and (*a*) silver nitrate solution, (*b*) alcoholic KOH, (*c*) ethyl alcohol.

102. Show how lactic acid can be made from propionic acid.

103. The silver salt of a tribasic acid was decomposed by heat. A sample of salt weighing 0.511 gram left a residue of silver weighing 0.322 gram. Calculate the molecular weight of the acid.

104. Write equations representing two methods for preparing hydroxy acids.

105. Outline methods for making (*a*) formic acid from oxalic acid, (*b*) oxalic acid from formic acid, (*c*) acetic acid from malonic acid, (*d*) malonic acid from acetic acid.

106. How could you distinguish between the compounds

(*a*) $C_2H_5 \cdot CO \cdot NH_2$ and $CH_3 \cdot CNOH \cdot CH_3$?
(*b*) $C_3H_7 \cdot CO \cdot OC_3H_7$ and $(C_3H_7 \cdot CO)_2O$?
(*c*) $CH_3 \cdot CHOH \cdot CO \cdot OC_2H_5$ and $CH_3 \cdot CH(OC_2H_5) \cdot COOH$?
(*d*) $CH_3 \cdot CO \cdot CH_3$ and $CH_3 \cdot CO \cdot OCH_3$?

107. By what chemical tests could you distinguish from each other

(*a*) $CH_3 \cdot CH_2 \cdot CH(COOH)_2$ and $CH_3 \cdot CH(COOH) \cdot CH_2 \cdot COOH$?
(*b*) $CH_3 \cdot CHOH \cdot COOH$ and $CH_3 \cdot CH_2 \cdot COOH$?
(*c*) $CH_3 \cdot CHOH \cdot CH_2 \cdot COOH$ and $CH_3 \cdot CH_2 \cdot CHOH \cdot COOH$?

108. An excess of ammonium oxalate was added to 50 cc. of a calcium chloride solution. The precipitated calcium oxalate was dissolved in sulphuric acid and titrated with potassium permanganate (3 grams $KMnO_4$ per liter). If 35 cc. of the permanganate solution was used, calculate the normality of the $CaCl_2$ solution.

109. What methods are known for resolving racemic mixtures into optically active components?

110. Show how fumaric acid may be converted into (*a*) succinic acid, (*b*) monobromsuccinic acid, (*c*) dibromsuccinic acid, (*d*) tartaric acid.

111. What products are formed in the hydrolysis of (*a*) C_2N_2, (*b*) CH_3CN, (*c*) CH_3NCO, (*d*) CH_3CONH_2, (*e*) CH_3NC?

112. Define (*a*) oxidation, (*b*) reduction, (*c*) substitution, (*d*) addition, (*e*) condensation, (*f*) racemization, (*g*) hydrolysis.

113. Give two methods for distinguishing between the isomers RCN and RNC.

114. What tests could you apply to show whether a pure substance is an alcohol or an acid? an unsaturated or saturated hydrocarbon? a ketone or an ether? an ester or an aldehyde? a nitro compound or an amine?

115. Write three possible structures for compounds having the formula C_4H_7OCl. Outline chemical reactions that may be used to identify each compound.

116. Write the structural formula of (*a*) a fat, (*b*) a lecithin. What products would each yield if saponified?

117. One gram of glucose, when added to an excess of Fehling's solution, and heated for twelve to fourteen minutes on the water bath, precipitated 1.3 grams of cuprous oxide. Compare this value with that calculated, assuming the glucose to be oxidized to gluconic acid.

118. Indicate chemical reactions that may be used to distinguish between

(*a*) CH_3COCl and CH_3CH_2Cl,
(*b*) $CH_3CH_2NH_2$ and CH_3CONH_2,
(*c*) C_6H_5Br and C_2H_5Br,
(*d*) $C_6H_5NH_2$ and $C_2H_5NH_2$,
(*e*) $C_2H_5OC_2H_5$ and $C_2H_5COOCH_3$,
(*f*) sucrose and glucose.

119. Write equations for (*a*) the fermentation of glucose, (*b*) the action of phenylhydrazine on glucose, (*c*) the oxidation of glucose by Fehling's solution.

120. One gram of a given sample of acetic anhydride neutralized 21.5 cc. of 1.0 normal NaOH. Five grams of this anhydride was added to two grams of pure glucose, and after the acetylation was complete the excess acid anhydride was found to neutralize 53.7 cc. of 1.0 normal NaOH. If the molecular weight of glucose is 180, how many hydroxyl groups are in the molecule?

121. What are the hydrolysis products of (*a*) sucrose, (*b*) starch, (*c*) lactose, (*d*) inulin, (*e*) glycogen, (*f*) maltose?

122. Devise a method for estimating the quantity of each of the carbohydrates in a mixture containing glucose, starch, and cellulose.

123. With the aid of any necessary inorganic reagents, but using no other organic substance, show by equations how it would be possible to prepare (*a*) ethylacetate from alcohol; (*b*) acetyl chloride from ethyl acetate; (*c*) formaldehyde from methyl alcohol.

124. Explain in detail the action of an excess of phenylhydrazine on dextrose.

125. Show how (*a*) dextrose may be converted into lævulose; (*b*) lævulose into dextrose; (*c*) a hexose into a pentose; (*d*) a pentose into a hexose.

126. Calculate the osmotic pressure at 20° of a solution containing 3.42 grams of sugar, $C_{12}H_{22}O_{11}$, in 90 grams of water.

127. A 10 per cent solution of a substance in a 20-centimeter tube produces an optical rotation of + 14°. Calculate its specific rotation.

128. What volume of nitrogen measured at 20° and 760 mm. will be obtained when an excess of alkaline sodium hypobromite acts upon 2 grams of urea?

129. What volume of nitrogen at 18° and 740 mm. will be obtained from 1.62 grams of amyl amine and an excess of nitrous acid?

130. Is phosgene an acid chloride? How does it react with water, with ammonia, and with alcohol?

131. Review the evidence in support of the accepted structure of uric acid.

132. What volume of nitrogen at 0° and 760 mm. is liberated when an excess of nitrous acid acts upon 0.6 gram of urea? What volume of carbon dioxide is formed in the same reaction? How are the two gases separated? How are they estimated quantitatively?

133. Specify the conditions that determine whether one should use vacuum distillation, steam distillation, or ordinary distillation in the purification of a liquid.

134. What is the mol fraction of water in a solution containing equal weights of alcohol and water?

135. How could you distinguish between the compounds

(*a*) $ClCH_2—CONH_2$ and $NH_2CH_2—COCl$?
(*b*) $CH_2OH—CH_2OH$ and $CH_3—COOH$?
(*c*) $CH_3—CO—CHCl_2$ and $CH_3—CCl_2—CH_2OH$?
(*d*) $CHCl_2—CH_2—CH_3$ and $CH_2Cl—CH_2—CH_2Cl$?

136. Write a structural formula for a polypeptid consisting of at least five of the amino acids found in proteins.

137. Beginning with acetic, propionic, and phenylacetic acids and any necessary reagents, show how a tripeptid having the following formula can be made:

$$C_6H_5—\underset{\displaystyle NH_2}{\underset{|}{CH}}—CO—NH—CH_2—CO—NH—\underset{\displaystyle CH_3}{\underset{|}{CH}}—COOH$$

138. Explain the fact that proteins are amphoteric.

139. Make a plan for isolating the hydrolysis products of simple proteins.

140. A liquid is known to be a hydrocarbon. Give qualitative tests that will determine whether it is a paraffin, an unsaturated aliphatic hydrocarbon, or an aromatic compound.

141. The density of benzene, C_6H_6, at 27° is 0.87. A solution of 12.8 grams of naphthalene in 390 grams of benzene has an osmotic pressure of 5.48 atmospheres at 27°. Find the molecular weight of naphthalene.

142. Write structural formulas for all compounds having the empirical formula C_8H_{10}. Devise experimental methods for distinguishing and identifying them.

143. Outline a method for preparing each of four compounds having the formula C_7H_7Cl.

144. Devise methods for making the following compounds from benzene: (*a*) meta-dichlorbenzene, (*b*) ortho-nitrophenol, (*c*) para-toluidine.

145. Two compounds have the formula C_8H_{10}. One of them yields two mononitro derivatives, the other only one. On oxidation each yields an acid which has the formula $C_8H_6O_4$. Write structural formulas for the two hydrocarbons.

146. Indicate the products formed by the reduction of nitrobenzene (*a*) in acid solution, (*b*) in alkaline solution.

147. Explain the action of nitrous acid on ethylamine, $C_2H_5NH_2$, and on aniline, $C_6H_5NH_2$, in hot and in cold solutions.

148. What chemical reactions could be used to distinguish between aniline and amyl amine?

149. How would you distinguish between acetanilide and acetamide?

150. A compound, on hydrolysis, readily gives aniline and acetic acid in equivalent proportions. Write the structural formula of the compound.

151. One equivalent of HCl completely dissolves and neutralizes one equivalent of $Ca(OH)_2$, but to dissolve one equivalent of diphenylamine, a large excess of acid is required. Explain.

152. If given a pure substance, how would you determine whether it is an aromatic amine or an aromatic nitro body? an ester or an ether? an unsaturated hydrocarbon or a saturated hydrocarbon? a phenol or an alcohol? an aromatic primary amine or an aliphatic primary amine?

153. What tests may be used to distinguish between primary, secondary, and tertiary amines? primary, secondary, and tertiary alcohols? alcohols and phenols? aliphatic and aromatic amines?

154. Prepare a chart of the oxidation products of aniline and the reduction products of nitrobenzene. Specify the reagents used in passing from aniline to nitrobenzene and from nitrobenzene to aniline.

155. Write equations representing a method for replacing a hydrogen atom in benzene by each of the following: (*a*) OH, (*b*) NH_2, (*c*) COOH, (*d*) NO_2, (*e*) Br, (*f*) C_2H_5.

156. Write equations representing the reactions between phenol and the following reagents: (*a*) KOH, (*b*) HNO_3, (*c*) Br_2, (*d*) CH_3COCl.

157. Calculate the quantities of hydrochloric acid and sodium nitrite required to convert 75 grams of aniline into phenol. What volume of nitrogen measured at 40° and 750 mm. will be evolved in the process?

158. Explain the fact that phenol precipitates as an oil when a solution of sodium phenolate is saturated with carbon dioxide.

159. Phenol has acidic properties and sodium phenolate is not volatile, but to prevent the steam distillation of phenol from aqueous solution, a large excess of NaOH is necessary. Explain.

160. How would you obtain phenol from a mixture of phenol and hydrocarbons, when the boiling points are such that they cannot be separated by fractional distillation?

161. Devise methods for making the following compounds from benzene: (*a*) meta-dibrombenzene, (*b*) ortho-nitrophenol, (*c*) para-xylene.

162. Outline a laboratory process for preparing benzenesulphonic acid. How is it obtained free from sulphuric acid?

163. How is benzenesulphonyl chloride prepared? How does it react with amines?

164. Phenylisocyanate was heated with one mol of ethyl alcohol, and a product finally isolated and recrystallized from alcohol which melted at 51.5° and contained 8.4 per cent nitrogen. What is it? Describe briefly an experiment by which you could prove that the compound contains a phenyl group attached to nitrogen.

165. Show by means of equations how the following compounds may be converted into benzene: (*a*) $CH_3 \cdot C_6H_5$, (*b*) $C_6H_5 \cdot COOH$, (*c*) $C_6H_5 \cdot NH_2$, (*d*) $C_6H_5 \cdot CO \cdot NH_2$, (*e*) $C_6H_5 \cdot NO_2$.

166. How may toluene be converted into benzyl chloride? into benzyl alcohol? into benzoic acid? into benzene?

167. Three different dichlorbenzoic acids, when heated with soda lime, yield the same dichlorbenzene. Write the structural formulas of the three acids.

168. Show by means of equations the steps involved in making benzoic acid (*a*) from toluene, (*b*) from benzaldehyde, (*c*) from benzonitrile.

169. Make plans for separating mixtures of (*a*) phenol and aniline, (*b*) phenol and benzene, (*c*) aniline and nitrobenzene, (*d*) phenol and benzoic acid.

170. Beginning with benzene and any necessary reagents, show by balanced equations how the following compounds may be made:

(*a*) $C_6H_5NO_2$, (*f*) $C_6H_5CH_3$,
(*b*) $C_6H_5NH_2$, (*g*) $C_6H_5—N=N—C_6H_4OH$,
(*c*) C_6H_5I, (*h*) $(C_6H_5)_3CH$,
(*d*) $C_6H_5SO_3H$, (*i*) $CH_3—C_6H_4—NH_2$,
(*e*) C_6H_5OH, (*j*) $C_6H_5—CO—C_6H_5$.

171. State two reactions of each of the following classes of compounds: acids, alcohols, esters, ketones, aldehydes, phenols, amines, amides, nitriles, diazonium salts.

172. Indicate by equations or in words a method of obtaining (*a*) a ketone from a secondary alcohol; (*b*) an acid chloride from an acid; (*c*) a phenol from a primary aromatic amine; (*d*) a monosaccharide from a disaccharide.

173. Write structural formulas for all acids having the formula $C_6H_5 \cdot C_3H_4 \cdot COOH$. Outline a method for preparing each.

174. Explain the relative and absolute methods of determining orientation.

175. Write equations representing a method for replacing a hydrogen atom in benzene by each of the following: (*a*) CN, (*b*) Cl, (*c*) COOH, (*d*) CH_3, (*e*) $N{=}N{-}\phi$.

176. Show by means of equations how the following compounds may be converted into benzene: (*a*) $CH_3 \cdot C_6H_5$, (*b*) $C_6H_5 \cdot COOH$, (*c*) $C_6H_5 \cdot NH_2$, (*d*) $C_6H_5 \cdot CO \cdot NH_2$, (*e*) $C_6H_5 \cdot NO_2$.

177. Beginning with benzene and any necessary reagents, show by means of balanced equations how benzidine is made.

178. Beginning with benzene, outline a method for synthesizing dimethylaminoazobenzene, $C_6H_5 \cdot N_2 \cdot C_6H_4N(CH_3)_2$.

179. Outline a method for preparing $C_{10}H_7 \cdot N{=}N \cdot C_6H_4 \cdot NH_2$. Begin with benzene, naphthalene, and any inorganic reagents.

180. Show how the diazo reaction may be used to convert aniline (*a*) into C_6H_5OH, (*b*) into C_6H_5Br, (*c*) into C_6H_5COOH, (*d*) into $C_6H_5 \cdot N{:}N \cdot C_6H_4OH$.

181. Write balanced equations showing how aminoazobenzene is made from benzene.

182. In the preparation of an azo dye what effects are produced by excess of nitrous acid? by high temperature? by high hydrogen ion concentration?

183. Indicate by means of structural formulas the reactions of triphenylmethane dyes with acids and with bases.

184. Outline a method for preparing (*a*) an azo dye, (*b*) a triphenylmethane dye.

185. Discuss the preparation and properties of triphenylmethyl.

186. Write equations for five reactions of the diazonium salts.

187. Prove the structure of one of the following alkaloids: (*a*) atropine, (*b*) coniine, (*c*) nicotine.

188. Tabulate the molecular structures that are susceptible to hydrolysis.

189. Outline by equations how you could prepare from benzene each of the following compounds: (*a*) $NH_2C_6H_4SO_3H$ (para), (*b*) C_6H_5OH, (*c*) $C_6H_5N_2C_6H_4OH$ (para), (*d*) $SC(NHC_6H_5)_2$.

190. The following neutral substances are each heated with dilute sodium hydroxide under a reflux condenser, and the resulting solution subjected to steam distillation. What product would you expect to find (1) in the distillate, (2) remaining in the distilling flask, — (*a*) ethyl acetate, (*b*) acetanilide, (*c*) methyl acetoacetate, (*d*) phenyl acetate, (*e*) valeric anhydride?

191. List three examples of keto-enol tautomerism.

192. Discuss the preparation, properties, and uses of acetoacetic ester.

193. Write equations showing how the following compounds may be obtained by means of the acetoacetic ester synthesis:

$$(a)\ CH_3 \cdot CO \cdot CH\begin{matrix} \diagup CH_3 \\ \diagdown CH_3 \end{matrix} \qquad\qquad (b)\ \begin{matrix} C_3H_7\diagdown \\ C_2H_5\diagup \end{matrix} CH \cdot COOH$$

194. Show how the malonic ester synthesis may be employed in the preparation of methylisopropyl acetic acid:

$$\begin{array}{lll} CH_3\diagdown & & \\ & CH—CH—COOH & \\ CH_3\diagup & \quad\;\; | & \\ & \quad CH_3 & \end{array}$$

195. Write equations indicating the use of malonic ester in preparing

(*a*) $(CH_3)_2CHCH_2COOH$,
(*b*) $CH_3CH_2CH_2COOH$,
(*c*) $(C_2H_5)(CH_3)CH \cdot COOH$.

196. Show how malonic ester may be used in the synthesis of amino acids.

197. What products would be obtained on the oxidation of methylethyl ketone, diethyl ketone, and methylisobutyl ketone?

198. Use Thiele's theory of partial valence to explain why bromine attaches to the β-carbon atom when an α-β unsaturated acid is treated with hydrogen bromide.

199. Show how the Grignard reaction may be used in the synthesis of (*a*) acids, (*b*) primary alcohols, (*c*) tertiary alcohols.

200. Outline methods for preparing the following compounds from acetone: (*a*) $CH_3—C \equiv CH$, (*b*) $(CH_3)_2COHC_3H_7$, (*c*) $(CH_3)_2COHCOOH$.

201. Indicate the action of the Grignard reagent upon (*a*) a ketone, (*b*) an ester, (*c*) an amine, (*d*) an alcohol.

202. Write balanced equations for all operations involved in making propionic acid by a method involving either the malonic ester synthesis or the Grignard reaction.

203. From acetone how would you prepare

(*a*) $(CH_3)_2C(OH) \cdot COOH$?	(*d*) $(CH_3)_2CHOH$?
(*b*) $CH_3 \cdot CCl_2 \cdot CH_3$?	(*e*) $CH_3 \cdot CH : CH_2$?
(*c*) $CH_3 \cdot CCl : CH_2$?	(*f*) $(CH_3)_3C \cdot OH$?

204. Show how the Friedel and Crafts reaction may be used in the preparation of (*a*) $C_6H_5 \cdot CO \cdot CH_3$, (*b*) $CH_3 \cdot C_6H_4 \cdot C_2H_5$, (*c*) $(C_6H_5)_3CH$.

205. Write equations for reactions by which C_2H_5CHO may be converted into (*a*) $C_2H_5 \cdot CHOH \cdot C_2H_5$, (*b*) $C_2H_5 \cdot CO \cdot C_2H_5$, (*c*) $C_2H_5 \cdot COOH$.

206. List all available methods for increasing the number of carbon atoms in a molecule by direct union of carbon to carbon.

207. Outline a method for converting propionic acid into acetic acid.

208. Beginning with acetone and any necessary reagents, show how the following compounds may be made: (*a*) secondary propyl alcohol, (*b*) pinacol, (*c*) tertiary butyl carbinol.

209. Give two or more examples of intramolecular rearrangement involving the shift of an atom or group from nitrogen to carbon. State how the transformation is induced in each case.

210. Write structural formulas for the compounds that may be derived from $C_6H_5 \cdot CO \cdot C_6H_4 \cdot CH_3$ through the action of NH_2OH and the Beckmann rearrangement.

211. A substance having a molecular weight of 180 is insoluble in water; it is mixed with water and distilled. At the temperature of distillation the partial vapor pressure of the substance is 60 mm., while that of the water is 700 mm. Calculate the weight of the substance which will distill over with 1 gram of water.

212. Substance A boils at 120°; substance B boils at 80°. A mixture of 85 per cent A and 15 per cent B boils at 130° (a maximum). Show by means of a diagram the courses that will be followed in distilling (a) a mixture containing 50 per cent A and 50 per cent B, (b) a mixture containing 90 per cent A and 10 per cent B.

213. Ten grams of a substance is dissolved in 100 cc. of water. It is four times as soluble in ether as in water. How much of the substance will be removed from the water by one extraction with 50 cc. of ether? by two extractions with 25 cc. of ether?

214. Two solvents, A and B, immiscible with water, are to be used in extracting a substance, C, from water. The solubility ratios are:

$$\frac{C_A}{C_W} = 2 \quad \text{and} \quad \frac{C_B}{C_W} = 5.$$

The concentration of C is 5 grams per 100 grams of water. (a) 105 grams of the aqueous solution is shaken with 100 cc. of A; calculate the concentration of the solute in the water layer. (b) 105 grams of the aqueous solution is shaken with 50 cc. of B; calculate the concentration of solute in the water layer.

215. A 50 per cent mixture of alcohol and ether boils at 45°. At that temperature the partial vapor pressure of ether in the mixture is 540 mm. Calculate the composition of the first fraction obtained when the mixture is distilled.

216. Chloroform ($CHCl_3$) boils at 61°. A solution of 0.3 gram of camphor ($C_{10}H_{16}O$) in 25 grams of chloroform boils at 61.3°. Calculate the value of the molecular elevation constant, K, for chloroform, and the heat of vaporization of chloroform.

217. Calculate the freezing point of a solution of 64 grams of naphthalene ($C_{10}H_8$) in 300 grams of benzene. What is the mol fraction of the solute?

218. At 27° C. and 1.5 atmospheres pressure, 0.4 mol of a gas has a volume of 6.56 liters. Find the value of the gas constant R.

219. Calculate the boiling point of a 10 per cent aqueous solution of sugar ($C_{12}H_{22}O_{11}$).

220. The relative lowering of the vapor pressure $\left(\frac{dp}{p}\right)$ caused by dissolving 2.45 grams of ethyl benzoate in 100 grams of benzene (C_6H_6) is 0.0124. Calculate the molecular weight of ethyl benzoate.

221. From the data concerning fluorbenzene given on page 459 plot molecular volumes as ordinates and temperatures as abscissæ. Extrapolate for volumes at any required temperatures and make the following calculations: (a) the molecular volume of benzene at 20° is 86.462; calculate its density at 30°; (b) the density of methyl alcohol at 15° is 0.798; find its specific volume at 35° C.

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